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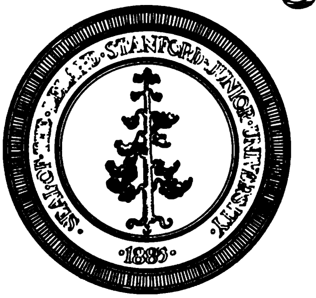
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A TEXT-BOOK OF ORGANIC CHEMISTRY

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A TEXT-BOOK

OF

ORGANIC CHEMISTRY

FOR STUDENTS OF MEDICINE AND BIOLOGY

BY

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PREFACE TO SECOND EDITION

THE reception which has been accorded this book has been such as to convince the author that the general plan of the work is sound. It has revealed the existence of a demand for a brief text-book which develops the theory of organic chemistry by the use of those compounds which have a biological interest.

Suggestions have come from several users of the book that its usefulness would be improved by the addition of an introductory chapter on purification and analysis of organic substances, and all have felt that the chemistry of the proteins should be given more extensive treatment.

Accordingly an introductory chapter has been included in this edition, and the more important features of the organic chemistry of the proteins has been developed in the concluding chapter. The treatment of this chapter is such as to prepare for a later course in physiological chemistry, and not an effort to treat the proteins from the standpoint which is logical in a text-book devoted to the latter subject. It is hoped that these modifications will add to the usefulness of the book as a text.

E. V. McCOLLUM.

BALTIMORE, MD.
January, 1920.

[illegible]

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INTRODUCTION

THE ELEMENTS WHICH ENTER INTO ORGANIC COMPOUNDS

THE element carbon is the basis of all the characteristic substances which occur in plant and animal tissues. Its most important property is that of combining with carbon, the atoms forming chains, which may be open, or closed into rings. No other element possesses this power in anything like the degree that carbon does. Chains containing scores of carbon atoms are known in some of the hydrocarbons which occur in petroleum. In these compounds carbon is always combined with hydrogen in definite proportions.

The simplest compounds of carbon are those with hydrogen. Substances composed entirely of these two elements are called *hydrocarbons*. Organic chemistry has been aptly defined as the study of the hydrocarbons and their derivatives. The several compounds which occur in gasoline and kerosene are hydrocarbons. Benzene, naphthalene, and oil of turpentine are other examples. A vast number of compounds contain carbon, hydrogen, and oxygen, familiar examples of this class being wood alcohol, grain alcohol, glycerol (glycerine), fats, acetic acid, tartaric acid, etc. A large group contains nitrogen as well as carbon and hydrogen, and in some cases oxygen as well. To this class belong urea, quinine, morphine, uric acid, etc. In addition to these elements chlorine, bromine, iodine, sulphur, and phosphorus are not uncommon as constituents of organic compounds. Less frequently, and always as the result of synthesis in the laboratory, compounds containing sodium, potassium, calcium, zinc, or other metals have been prepared. The latter are of the greatest importance in transforming certain types of organic compounds into derivatives of the most varied kinds.

Purification of compounds before attempting an analysis is of fundamental importance. In most cases this is accomplished by distillation or by crystallization of the substance, but in a few instances sublimation is possible. Crystallization is the most effective method of the three, so whenever it is possible to do so the chemist always tries to get a substance in which he is interested converted into a solid crystallizable derivative, provided it is not itself capable of being crystallized. After purification the original substance may be recovered by the decomposition of its derivative. For example, a certain acid which is a liquid and somewhat unstable, and not capable of distillation without decomposition, can be purified by conversion into a salt of some one of the metals or of one of the natural organic bases such as quinine, and, in the form of such salt, can be recrystallized repeatedly. When it is found by appropriate tests that purification has been effected, the salt is decomposed and the pure substance recovered.

Purity of a substance must be established either by repeated analysis of small samples following the application of some method of purification, or by the measurement of some physical property. The most convenient of these for measurement in organic compounds is usually the melting point or the boiling point. Both of these are highly characteristic and when once established serve thereafter the valuable purpose of identifying substances and establishing their purity.

Distillation. — When a mixture of compounds such as is found in petroleum is distilled from a flask containing a thermometer so placed as to insure that the bulb will be surrounded by the vapors of the distilling liquid, it is found that the mercury gradually rises as the distillation progresses. This is due to the fact that certain of the compounds in the petroleum boil, and therefore distill at lower temperatures than others, and those having the lowest boiling points pass over first, but tend always to pass over in a simpler mixture than that contained in the distilling flask. In this manner, by repeating the distillation of fractions which pass over within a range of a few degrees, these simpler mixtures can be separated into their constituents. When this is accomplished the product finally collected in the receiver will distill with the thermometer remaining almost constant during the distillation.

A pure substance boils at a constant temperature, unless it undergoes some decomposition at the boiling temperature. This leads one to conclude that the distillate which comes over while the thermometer records but a small variation of temperature is practically of constant composition. The problems of fractional distillation are, however, not so simple as this. The possibility of making a complete separation by means of distillation depends on whether the components of the mixture are (*a*) completely immiscible, (*b*) partly miscible, (*c*) miscible in all proportions.

When the components are completely immiscible, the vapor pressure of one remains uninfluenced by the presence of the other. This condition is approximated in the case of nitrobenzene and water. If the molecular weights and the vapor pressure of the components at the temperature of distillation are known, the composition of the distillate can be determined. If two components, A and B, have molecular weights and vapor pressures represented by M and M' and P and P', respectively, the ratio of A to B in the distillate will be $MP/M'P'$. Even though one liquid be more volatile than the other, which is usually the case, it usually also happens that the molecular weight of the less volatile one is much greater than that of the more volatile one, as in the case of water and nitrobenzene. The ratio just described need not therefore be very great and hence the less volatile liquid will come over in fair amount. It is under conditions such as these that steam distillation can be carried out effectively.

When a mixture of partially miscible liquids is distilled the composition of the distillate remains constant so long as there are two layers in the flask. These layers will consist of liquid A dissolved in liquid B and of B dissolved in A. Each of these solutions will emit vapors of the same composition, for the same vapor must be in equilibrium with both solutions. The composition of the vapor is not the same as either layer. When one of the layers disappears during the course of distillation, the remainder distills as does a completely miscible mixture.

Mixtures which are completely miscible do not all behave alike during distillation. One group of such substances is represented by solutions of nitric acid in water, or of hydrochloric acid in water. The vapor of water is readily soluble in nitric acid vapors, and the vapors of nitric acid are readily soluble in that of water. In such a system there will always exist a mixture the vapor pressure of which is lower than that of any other mixture. In any mixture of acid and water which is stronger than 68% acid, acid of greater strength than 68% will distill over until the solution remaining in the flask comes to a concentration of 68%, after which the latter strength of acid distills over constantly at a temperature of 126 degrees. In the case of hydrochloric acid and water the constant boiling mixture contains 20.2% of acid, and boils at 110 degrees C. Formic acid forms a similar constant boiling mixture.

In solutions the vapors of which are sparingly soluble in the liquids, there will exist a mixture, the vapor pressure of which is greater than that of any other mixture. On distilling such a mixture, of which propyl alcohol and water is an example, a constant composition distillate will be obtained *at first*, leaving behind in the flask a mixture of changing composition according to the proportions of alcohol and water which it contains.

When the vapor of one constituent (a) of a mixture of liquids is very soluble in the other (*b*), but the vapors of (*b*) are very sparingly soluble in (*a*) and the vapor pressure of (*a*) is greater than that of (*b*), the vapor pressures of mixtures of (*a*) and (*b*) will continually diminish as the composition of the mixture changes from 100 per cent (*a*) to 100 per cent (*b*). On distilling such a mixture pure (*a*) will first pass over, then a mixture of changing composition in which (*b*) continually increases, until finally the latter comes over pure. Mixtures of ethyl alcohol behave in this manner when distilled.

Crystallization is the most important method of purification of such substances as can be obtained in the crystalline form. During the formation of crystals the impurities which may be present in a solution of an impure substance tend strongly to remain behind in the mother liquor. The crystals which can be filtered off and washed with a suitable liquid are thus freed from contaminating substances as the process is repeated.

The readiness with which different substances crystallize differs greatly. When the process is difficult to start it may be hastened or facilitated by agitation, the addition of a crystal, or the addition of another solvent.

Nearly all substances are more soluble at high temperatures than at lower, and accordingly solutions which are saturated at their boiling points become supersaturated when cooled. This procedure is the most common one for obtaining crystals, a crop being obtained as a saturated solution cools. Crystals which are small are as a rule of greater purity than large ones.

Fractional crystallization is an important procedure for the separation of the components of a mixture of crystallizable substances. This method is applicable to substances having different solubilities. Each time a crop of crystals is obtained the component having the least solubility will predominate. The mother liquors will at the same time become richer in the second component having a lower solubility.

Melting Point. — The determination of the temperature at which a substance melts is the most convenient, and at the same time one of the most valuable, methods of determining the identity of a substance which exists in the crystalline form, or of establishing its purity for purposes of analysis. The presence of impurities causes a substance to melt at a lower temperature than it does in a pure state. Since several substances may have the same or nearly the same melting temperature, the determination of the latter is, alone, not sufficient to establish the identity of a substance. In order to make sure of the identity it is customary to secure data by analysis to show the percentage composition with respect to carbon, hydrogen, and any other elements which the compound may contain except oxygen. The latter element is not readily estimated quantitatively, and it has always remained customary to determine it by difference. Accordingly the difference between the sum of all the elements which can be identified and estimated, and one hundred, is accepted as representing the oxygen content.

There is a very simple test which is accepted by organic chemists as affording conclusive evidence of the identity of a substance. Suppose a substance is known and its properties are all carefully measured and tabulated in reference books, and among these properties is the melting point. It is desired to identify a sample of this substance, and after a preliminary purification its melting point is taken as shown in Fig. 1. The melting point may agree with that which the new substance is suspected to be. If now some of the substance to be identified is mixed with a small portion of pure material from a known sample, and the mixture is again melted, and the melting point of the mixture is the same as that of each of the samples before mixing, there can be no doubt whatever about the identity of the substance under investigation.

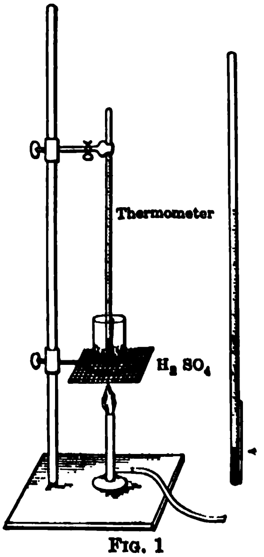


FIG. 1

Great dependence is placed by chemists in the reliability of this simple test. It depends on the general law that mixtures of substances always possess a lower melting point than either alone. It is a valuable asset to a laboratory of organic chemistry to have available as large a museum of samples of compounds of known purity as possible for comparison with samples of unidentified substances which it may be desired to identify.

Crystalline Form is frequently of value in the identification of organic substances. It is, however, less reliable than melting point or boiling point, for the form in which a substance crystallizes frequently varies in the presence of impurities. The kind of solvent from which a compound separates likewise may determine the crystalline form, so this property possesses but limited usefulness, and must be used with judgment. It is not customary in laboratories of organic chemistry to maintain apparatus for the measurement of the angles of crystalline substances. In the hands of an expert crystallographer, the comparison of the crystalline form of a known with a suspected sample of a substance, the history of the crystallization of which is known, forms one of the best criteria in cases of difficult identification.

Odor and Color are of great value to the organic chemist in the identification of substances. The odors of many substances are so characteristic that once smelled they can thereafter be recognized readily. This sense cannot of course be depended on as a criterion of purity, except in connection with establishing the absence of certain impurities which themselves have recognizable odors.

Special attention should be given by the student to fixing in the memory the appearance of each of the substances which he handles in the laboratory. Look at details, and learn their significance. Ability to see little things, and distinguish small differences of any kind, between samples of the same or different substances, makes the difference between being master of a new chemical problem, or of being helpless before it.

Specific Gravity, when taken with sufficient accuracy, is very valuable for establishing the identity of a substance, either organic or inorganic. The preparation which is used for this purpose must of course be pure.

Optical Properties. — Certain organic as well as inorganic compounds possess the property of rotating the ray of polarized light either to one or the other hand, and the extent to which they are able to do this is characteristic for the substance. Where but one compound having this optical property is present in a mixture it is possible to determine it quantitatively in the presence of other substances with accuracy. This is now regularly done in the estimation of the amount of cane sugar or beet sugar in solutions obtained in factories by pressing the juice out of the cane or beets.

QUALITATIVE DETECTION OF THE ELEMENTS IN A COMPOUND

Carbon. — All organic compounds burn when heated to a sufficiently high temperature in the air. The carbon and hydrogen combine with the oxygen of the air to form carbon dioxide and water respectively. Benzene, the molecule of which contains six atoms of carbon and six atoms of hydrogen, can be burned according to the following equation:

$$C_6H_6 + 15\ O = 6\ CO_2 + 3\ H_2O.$$

Benzene burns in the open air with a smoky flame because the carbon is partly deposited unburned in the form of soot. In order to make it burn completely benzene must be burned in a special apparatus in which this deposited carbon can be heated in contact with the oxygen of the air until it is oxidized. The deposit of black soot is itself a test for carbon.

The carbon dioxide formed can be conveniently tested for by passing the gases formed during combustion of a compound through limewater or barium hydroxide. In the former a precipitate first forms, which later dissolves if an excess of carbon dioxide is added. In the latter the precipitate which forms is permanent.

Hydrogen. — When the products of the combustion of an organic compound are brought into a cooled vessel, the water which has been formed from the oxidation of the hydrogen in the compound condenses to the liquid state and becomes visible. This forms a test for the element hydrogen. Many organic compounds such as sugar, albumen, starch, etc., when heated in a test tube, lead to the formation of drops of moisture in the upper, cooler parts of the tube.

Nitrogen. — Organic substances which contain nitrogen are decomposed when heated in the presence of alkalies, with the formation of ammonia from a considerable amount of the nitrogen which they contain. When such substances as albumen, urea, etc., in intimate contact with soda lime (a mixture of sodium hydroxide and quick lime), are heated in a test tube ammonia is given off as a gas. This can be readily identified by its odor and by its property of turning moist red litmus paper blue.

Chlorine. — Organic compounds which contain chlorine *or other halogen*, are decomposed by heating with soda lime, the halogen uniting with the sodium and calcium to form the chlorides of these metals. In order to test for the halogen the soda lime is dissolved in water, acidified with nitric acid, and silver nitrate added. The formation of the characteristic silver chloride, insoluble in nitric acid, is characteristic.

Sulphur. — Organic substances which contain sulphur are decomposed by heating in a test tube along with a piece of metallic sodium. The carbon cannot be all burned under these conditions, but the sulphur combines with the sodium to form sodium sulphide. The tube is heated cautiously until the sodium takes fire. After the flame is extinguished the tube is heated strongly in a gas flame, then when glowing, the tube is touched to the surface of a small amount of water contained in a beaker. The glass is shattered and the contents of the tube are broken up somewhat to facilitate the solution of any sodium sulphide which has been formed. The clear solution is treated with a few drops of a very dilute solution of sodium nitroprusside. The formation of a deep violet color denotes the presence of sulphur.

Phosphorus. — In order to test for the element phosphorus in organic compounds it is necessary to so decompose the substance as to convert the phosphorus into phosphoric acid, H_3PO_4, which is then tested for by the methods of inorganic qualitative analysis. The most convenient way to do this is to heat the substance under investigation in a crucible with a liberal amount of a mixture of sodium carbonate (1 part) and potassium nitrate (2 parts). The sodium carbonate should be anhydrous. This mixture is strongly oxidizing because the nitrate decomposes readily with the liberation of oxygen. The mixture should be heated until it is almost white. (Carbon all oxidized to CO_2.)

When cool the contents of the crucible are dissolved in a little hot water and transferred to an evaporating dish. Hydrochloric acid is added to the neutral point. The presence of phosphoric acid may now be established in either of two ways: (1) The solution may be made strongly alkaline with ammonia, and magnesia mixture added. A white crystalline precipitate of magnesium ammonium phosphate indicates phosphorus. Magnesia mixture is composed of magnesium chloride, ammonium chloride, and ammonium hydroxide. (2) Nitric acid may be added to the solution until it is strongly acid, then an equal volume of ammonium molybdate solution added. The formation of a fine yellow precipitate on warming at 60 degrees serves as a test for phosphorus. The precipitate is ammonium phosphomolybdate.

FINDING THE EMPIRICAL FORMULA OF AN ORGANIC COMPOUND

When a substance has been examined as to its appearance, odor, crystalline form, melting point or boiling point as the case may require, whether the substance is acid or basic, etc., it is frequently possible for a well-trained chemist to decide the nature of the compound, for many thousands of organic compounds have been exhaustively studied and their properties described. These data are available for easy reference in various dictionaries and larger works in all laboratories and are frequently consulted by chemists who are studying unknown substances.

Not only are the physical and chemical properties of all these compounds known, but in many instances the *structure of the molecule* as well. Among organic compounds there are acids and bases and many other classes which cannot be appreciated until the subject has been logically developed. These include aldehydes, alcohols, ketones, bodies whose peculiar chemical properties depend on the architecture of the molecule, or, expressed in another way, their chemical properties depend on the way the atoms of the several elements are grouped in the molecule.

In the study of a substance which has not been thoroughly investigated the procedure universally adopted by chemists, after the usual preliminary observations, is to determine qualitatively the elements in the substance, and then the *empirical formula.* The latter indicates the number of each of the different kinds of atoms in the molecule. Thus acetic acid may be expressed in formula in two ways: $C_2H_4O_2$ or CH_3COOH. The former is the empirical formula since it tells us that acetic acid consists of a group of eight atoms, two of carbon, four of hydrogen, and two of oxygen. This formula tells nothing of the nature of the substance. The second formula, CH_3COOH, is the *structural formula.* It expresses in a kind of shorthand a number of *properties* to those who know this language. Among other things it indicates that it is an acid, and will taste sour, turn blue litmus paper red, and form salts with one equivalent of metal.

In order to determine the empirical formula of a compound it is necessary to make an accurate quantitative determination of each of the elements which make up its molecule, so that these can be expressed in percentages of the substance. In order to do this it is necessary to decompose the substance quantitatively into known substances which are of such a nature that they can be easily collected and weighed. From this data the weight of each of the elements in the compound are calculated.

Quantitative Analysis for Carbon and Hydrogen. — Carbon and hydrogen in the substance to be analyzed are converted quantitatively into carbon dioxide and water respectively and these are collected in suitable devices for accurate weighing. The apparatus which serves this purpose is illustrated in Fig. 2. It consists of a hard glass tube about 85 cm. long and 12–15 mm. outer diameter, open at both ends and made of very difficultly fusible glass. Quartz tubes for this purpose have been available for several years and are superior to glass because of their high fusibility. The tube is thoroughly cleaned and filled as shown in Fig. 2. Five centimeters at either end are left empty (*A*). Then in the end to the left (*B*) a 15-cm. spiril of copper gauze, the surface of which has been oxidized by heating in air or oxygen, is inserted. In front of this is a free space of about 10 cm., then a short copper gauze spiril (*D*). To the right of this is a space of about 40–45 cm., which is filled with coarse particles of copper oxide (*E*) which is held in place by another copper gauze spiril (*F*). The remainder of the tube

(*G*), which should not be longer than 5 cm., is free except for a cork by which it is connected with the absorption apparatus.

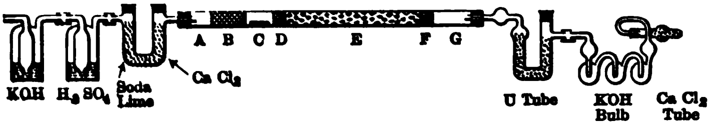


FIG. 2

Copper oxide is easily reduced in the presence of easily oxidizable substances. This means that it readily gives up its oxygen for the combustion of the substance, and is changed into metallic copper. The substance to be analyzed is weighed and placed in a porcelain or platinum boat which is inserted into the tube at (*C*). To do this it is necessary to remove the gauze (*B*). The object is now to burn completely the sample of material and to collect the combustion products quantitatively for weighing.

Most substances are burnable in air and during the combustion of the substance a very slow current of air is drawn through the apparatus. This must be passed through a set of reagents to free it entirely from carbon dioxide and water, since these are the products which are to be secured from the analysis and weighed and no source of them other than the sample under examination is permissible. The air is freed from carbon dioxide and moisture by passing it first through a wash bottle containing a strong solution of potassium hydroxide, then dried by passing through a similar bottle of strong sulphuric acid. As a further safeguard the air is passed through a U-tube containing soda lime in the first arm and calcium chloride in the second.

At the forward end of the combustion tube is an absorption apparatus consisting of a U-tube filled with granulated calcium chloride and a potash bulb containing a strong solution of potassium hydroxide. Beyond this is a small calcium chloride tube to catch any water which may be removed from the potash bulb by the passage of dry gas through it.

The first calcium chloride tube, the U-tube, absorbs all the water from the air which is passed through the apparatus. All of this water is formed from the combustion of the hydrogen of the compound being analyzed, since the air which enters the apparatus is rendered entirely dry by the reagent through which it is passed before entering the tube. The calcium chloride does not absorb carbon dioxide, however, and this passes on to the potash bulb and is absorbed and held as potassium carbonate.

The process of combustion is carried out very slowly. The copper oxide in the forward part of the tube is first heated to redness, then the spiril gauze behind the boat containing the sample is heated, and finally heat is applied to the region of the tube where the boat is located, but with caution in order not to burn the substance too rapidly. If heated too quickly a sufficient volume of gas is liable to be formed to force the gases through the heated copper oxide so quickly that they would not all be oxidized. Under these circumstances the analysis would be spoiled. When the carbon has all been oxidized, as is seen by the freedom of the boat from black deposit of the charred sample, the heating of the tube is continued for some time, and the current of air is still drawn through it in order to be certain that the products of the combustion are all swept out and into the absorption apparatus. Finally the heat is removed from the apparatus and the absorption apparatus disconnected.

Before weighing, the U-tube and potash bulb and the safety tube of calcium chloride attached to it are allowed to cool. The gain in weight of the U-tube represents water formed from the combustion of the hydrogen of the substance analyzed, and the gain of the potash bulb and the safety tube beyond it represents the carbon dioxide formed from the combustion of carbon of the sample. From these weights the amount of carbon and hydrogen in the sample are calculated. The atomic weight of carbon is 12 and of oxygen 16. The per cent of carbon in carbon dioxide is therefore found by dividing 12 by the molecular weight of carbon dioxide, which is 44.

$$\tfrac{12}{44} = \tfrac{3}{11} \text{ or } 0.2727\ \%.$$

The per cent of carbon in the substance burned is found by the following formula:

$$\text{Per cent } C = \frac{\text{wt. of CO}_2\text{ produced} \times 3 \times 100}{11 \times \text{wt. of substance burned}}.$$

One ninth of the weight of water to which the increase in weight of the U-tube is due is hydrogen. The per cent of hydrogen in the substance burned is found by the following formula:

$$\text{Per cent } H = \frac{\text{wt. of water produced} \times 100}{9 \times \text{wt. of substance burned}}.$$

When qualitative analysis has shown that the substance does not contain nitrogen, sulphur, phosphorus, or the halogens, and the ignition of a tiny bit on a platinum foil shows that there is no inorganic element (which would remain as ash) the sum of the per cents of hydrogen and carbon deducted from 100 gives the per cent of oxygen. There is no satisfactory way known to determine the content of oxygen in an organic compound directly and quantitatively. It is therefore determined as above described and is said to be *determined by difference.*

In case the substance which is being analyzed for carbon and hydrogen contains nitrogen it is necessary to adopt a special procedure in the combustion. Oxides of nitrogen are formed which would be absorbed by the potash and would be weighed as carbon dioxide. In order to obviate this difficulty a copper spiril, the surface of which contains no oxide, is placed in the forward end of the combustion tube just before the absorption apparatus. This spiril is reduced to metallic copper by heating in a gas flame and then inserting into a tube containing alcohol. The alcohol *reduces* the oxides of copper and is itself oxidized in the process. The oxides of nitrogen formed from the nitrogen of the substance under analysis are reduced to elemental nitrogen when they come into contact with the hot copper spiril. It is necessary, when this modification of the method is employed, to shut off the air current through the combustion tube during the burning of the sample. After this is completed the air current is turned on to sweep out the products of combustion of the sample.

[illegible] analysed contains sulphur [illegible] to partly replace the [illegible] lead chromate. This is [illegible] effect the oxidation [illegible] hydrogen to H_2O, and will [illegible] phosphorus as lead sul- [illegible]

[illegible] the ultimate analysis of [illegible] is a laborious process and one [illegible] to carry through suc- [illegible] therefore resorted to only [illegible] the case of the investigation [illegible]

[illegible] in Organic Compounds. — [illegible] by a process similar to [illegible] estimation of carbon and [illegible] containing nitrogen, but with [illegible] A current of carbon [illegible] the apparatus instead of air, [illegible] free nitrogen and the object [illegible] the nitrogen in the substance [illegible] nitrogen and collect and [illegible] dioxide is generated by heat- [illegible] containing sodium bicarbonate, [illegible] anhydrous and on being heated [illegible] and is converted into the normal [illegible] passed through a wash bottle [illegible] acid to dry it before it [illegible] tube.

[illegible] forming and washing carbon diox- [illegible] The absorption apparatus for nitrogen consists of a gas burette, having a mercury valve and leveling bulb at the bottom. This apparatus is illustrated in Fig. 4. After a stream of carbon dioxide has been passed through the tube for some time, and the combustion tube is heated ready for the decomposition of the sample to be analyzed, the burette is filled with the 40% KOH solution contained in the leveling bulb, the stopcock closed, and the bulb quickly lowered to take the pressure off the inside of the hot and somewhat softened glass. If the air (nitrogen) has been entirely removed from the tube, the bubbles of carbon dioxide which enter the burette will be quickly absorbed and no

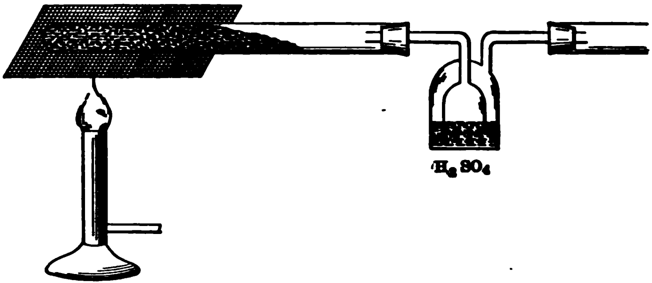


Fig. 3

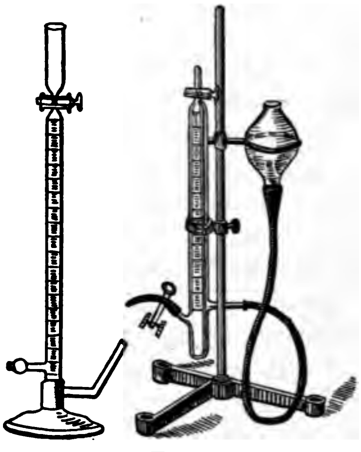


Fig. 4

gas will collect in the top of the burette. After this test has been made the heating of the sample to be analyzed is begun cautiously so as not to decompose it too rapidly. Nitrogen begins to collect in the burette and continues to do so until the burning is complete and the nitrogen formed is swept out of the combustion tube. When this point is reached the large bubbles of carbon dioxide which enter the burette at the bottom are again completely absorbed as they ascend, and the volume of gas in the burette no longer increases.

The heating is now discontinued, the burette being first disconnected. When the burette has cooled to room temperature the leveling bulb is raised so as to make the level of the solution it contains coincide with the surface of the solution in the burette, and the volume of gas is read off with care. A thermometer beside the apparatus is read at the same time, and the barometer reading showing atmospheric pressure is likewise secured. From these data the weight of the nitrogen derived from the substance analyzed is found by reference to a table. It is necessary to add to the barometric pressure the difference between the vapor pressure of water and that of 40 per cent KOH solution at the temperature at which the measurement is made. This difficulty is obviated by transferring the nitrogen gas to a measuring tube filled with water and immersed inverted in a cylinder full of water.

From the weight of nitrogen found by reference to a table the per cent of this element is calculated.

This method is now rarely used since it has been found that the estimation of the nitrogen in an organic compound can be effected much more easily and more accurately by the Kjeldahl method, in the case of nearly all compounds. There are a few substances, however, which cannot be accurately analyzed by the latter method, so the old and historic method is still the last appeal.

In the Kjeldahl method the substance to be analyzed is placed in a flask and treated with concentrated sulphuric acid. Potassium sulphate is added to raise the boiling point of the mixture, and a little copper sulphate to act as a catalyzer, and the whole is digested over a flame so adjusted as to keep the solution near the boiling point. At first the contents of the flask turn black owing to carbonization, but gradually it is all oxidized, forming carbon dioxide and water, which escape, and ammonia which remains in the flask in combination with the sulphuric acid as sulphate. The formation of ammonia is quantitative. Finally the contents of the flask are cooled, dissolved in water, made alkaline with sodium hydroxide, and distilled. The ammonia distills over and is collected in a measured amount of standard acid. The excess of acid is measured by titration and the amount of ammonia present calculated. From this the amount of nitrogen in the sample can be calculated.

Calculation of the Provisional Formula. — When the percentages of each of the elements in the compound are divided by their respective atomic weights, the ratios in which the atoms of the different elements occur in the molecule are discovered. Thus an accurate analysis of ethyl alcohol would give 52.18 % C; 13.04 % H; and 34.78 % of O.

$$52.18 \div 12 = 4.348 \qquad 4.348 \div 2.173 = 2.000$$
$$13.04 \div 1 = 13.040 \qquad 13.040 \div 2.173 = 6.000$$
$$34.78 \div 16 = 2.173 \qquad 2.173 \div 2.173 = 1.000$$

The ratios between the atoms of C, H, and O in the molecule are therefore as 2 : 6 : 1 and the formula of the compound might be C_2H_6O. There is still the possibility, however, that the formula may be some multiple of the simplest combination. This must be decided by a molecular weight determination.

In the case of easily volatile liquids the determination of the molecular weight may be done by the method of Victor Meyer. This is described in all textbooks of general chemistry. It rests on the comparison of the volume occupied by the vapor of a known weight of the substance under investigation, with the weight of an equal volume of air. According to the hypothesis of Avogadro, which has been verified in numerous ways, equal volumes of all gases under the same conditions of temperature and pressure contain the same number of molecules. Two grams of hydrogen, thirty-two of oxygen, seventeen of ammonia, twenty-eight of nitrogen, and forty-four of carbon dioxide, when measured at 0° and 760 mm. pressure, occupy the same volume, viz.: 22.4 liters.

The determination is carried out by vaporizing a known weight of the substance at a temperature well above the boiling point and measuring the volume of the gas produced under the conditions of the experiment. The changes in volume of a gas with changes of temperature and pressure are well known, and it is possible to calculate the amount of the substance under investigation which would give sufficient gas to occupy 22.4 liters under normal conditions, even though the substance is not a gas under these conditions.

Again considering the case of ordinary alcohol for which we have already deduced the provisional formula C_2H_6O. Without further data it would be impossible to tell whether this, or double, or any multiple of the formula actually represents the molecule. If we weigh out 0.1 gram of alcohol and vaporize it in the Victor Meyer apparatus, and apply the necessary calculations to show what volume the gas should occupy under standard conditions (0° C. and 760 mm. mercury) we should find that this volume would be about 48.7 cc. The following formula enables us to calculate the molecular weight of the substance :

$$0.1 : 48.7 :: x : 22{,}400.$$

$$x = \frac{22{,}400}{48.7} = 46.$$

The molecular weight of the substance alcohol is therefore by the vapor density 46. This corresponds to the formula C_2H_6O, and shows that the molecule is actually the simplest formula which we arrived at from the percentage composition, and not a multiple of it.

Determination of the molecular weight of a substance by the vapor density method is possible only where the substance is volatile without decomposition. It is possible, however, to determine the molecular weight of substances in solution, since there are close correspondences between the behavior of dissolved substances and those in the gaseous state. The methods of doing this belong in the field of general chemisty and need only be mentioned here.

It has been found that when substances are dissolved in water or other solvents, the solutions freeze at lower temperatures than the pure solvents. The degree to which the freezing point is depressed bears a direct relation to the amount of dissolved substance. The molecular weights of glycerol, glucose, and cane sugar are 92, 180, and 342 respectively. Water freezes at 0° C. when pure, but when the above weights of each of these three substances, called a gram molecule of each, are dissolved in a liter of water, three solutions are obtained which contain equal numbers of dissolved particles, but of different kinds. The freezing points of the three solutions are, however, the same. Each will freeze at 18.5° C. It is found that any weights of these substances which are proportional will produce a similar depression of freezing point. It is customary to work with much more dilute solutions in practice than the gram molecule per liter. The formula for the calculation of the molecular weight from the observed depression of the freezing point is the following:

$$M = \frac{100 \times g \times D}{s \times d}$$

where g equals the weight of the sample, s the weight of solvent in grams, d the observed depression of the freezing point, D the molecular depression, and M the molecular weight.

This method cannot be applied in the simple manner described for the determination of the molecular weight of most inorganic substances which when dissolved in water are dissociated electrolytically and conduct the electric current. The ions which are formed by the dissociation behave as independent particles, so the depression of freezing point is greater than the theoretical value.

In the case of many acids and bases it is only necessary to determine quantitatively some constituent of the molecule in order to deduce the molecular weight. Any acid, such as acetic for example, must have a molecular weight which will correspond with the percentage composition of its salts. The empirical formula of the acid is CH_2O. We might assume that its silver salt would be represented by the formula CHOAg. The theoretical per cent of silver in this complex would be expressed by the atomic weight of silver, 107.9, divided by the sum of the atomic weights CHOAg, which is 136.9. $\frac{107.9}{136.9} \times 100 = 78.8.$ The per cent of silver in silver acetate is, however, 64.6. This corresponds to a molecule double that given above, or $C_2H_3O_2Ag$. Actually the formula of acetic acid is CH_3COOH and its silver salt CH_3COOAg. The significance of this latter method of writing the formula will not be appreciated until the next chapter has been read.

In selected cases it is also possible and desirable to determine the molecular weight of a compound by the osmotic pressure which it exerts when in solution. In other cases the determination of the lowering of the vapor pressure of a solvent due to the effect of a dissolved substance may be used as a criterion of the size of the molecule.

A TEXT-BOOK OF ORGANIC CHEMISTRY

ORGANIC CHEMISTRY FOR STUDENTS OF MEDICINE

THE FATTY COMPOUNDS

CHAPTER I

THE SATURATED HYDROCARBONS

1. The simplest of the compounds composed of carbon and hydrogen is *methane*, CH_4. The compounds containing only these two elements are called hydrocarbons. It occurs widely distributed in nature, in the gases evolved from volcanoes, and in those which escape from coal mines, where it is called *fire damp*, and as the principal constituent of *natural gas*. Coal gas contains considerable amounts of this compound (30–40%), since it results from the destructive distillation of many kinds of organic matter. Methane also results from the degradation of vegetable matter, especially cellulose, by certain kinds of microörganisms. In this way it is produced by the fermentation of vegetable tissues under water in marshes, and derived its older name of *marsh gas* in this way. It is an ever present constituent of the gases in the intestines and is normally found in small amounts in the respired air, some of the methane produced by fermentation in the intestines being absorbed into the circulation and eliminated through the lungs.

Preparation:

(*a*) When a mixture of carbon monoxide and hydrogen is passed through a tube containing reduced nickel, heated to 200° C., there is produced methane and water:

$$CO + 3\,H_2 = CH_4 + H_2O$$

(*b*) At somewhat higher temperatures (230°–300° C.) carbon dioxide is likewise reduced by hydrogen in the presence of finely divided nickel, the latter undergoing no change:

$$CO_2 + 4\,H_2 = CH_4 + 2\,H_2O$$

(*c*) Hydrogen sulphide and carbon disulphide, when passed through a tube containing heated copper, react to form copper sulphide and methane:

$$2\,H_2S + CS_2 + 4\,Cu = 4\,CuS + CH_4$$

Other methods will be described for the formation of methane from certain of its *derivatives* later.

Properties: Methane is a colorless and odorless gas. Its specific gravity is 0.559, air being taken as 1. When subjected to a pressure of 140 atmospheres it liquefies at [illegible] Its boiling point is –162° C. and it solidifies at [illegible] The electric sparks from an induction coil decompose methane into carbon, which is deposited as a black soot and hydrogen gas. The strongest oxidizing agents, such as nitric and chromic acids, scarcely attack it, and concentrated sulphuric acid and alkalies have no action upon it. It is therefore one of the most stable and inert of chemical compounds. On being led through a red hot tube it is split up in part into its elements, carbon and hydrogen, but in part forms more complex hydrocarbons containing carbon chains, which will be described later (**6**). It burns with a faintly luminous flame. When mixed with air or oxygen it forms a violently explosive mixture, carbon dioxide and water being formed:

$$CH_4 + 2\ O_2 = CO_2 + 2\ H_2O$$

This is the reaction which occurs when the *fire damp* of mines explodes.

2. Formation of Derivatives of Methane. — Chlorine or bromine react with methane forming respectively chlor and brom methanes. Methane mixed with chlorine is easily exploded. If two atoms of chlorine (one molecule) be present in the mixture for each molecule of methane, the following products represent the principal reaction:

$$CH_4 + Cl_2 = \underset{\text{Methyl chloride}}{CH_3Cl} + HCl$$

The methane molecule less one H atom is known as the *methyl* group or radical.

Methyl chloride is a colorless gas of a pleasant ethereal odor which boils at −23.7° C. It is slightly soluble in water (4 volumes in 1 of H_2O) and can be easily freed from hydrochloric acid by washing. Methyl chloride is used for producing low temperatures artificially. When strongly compressed the volume of the gas is greatly decreased and it becomes hot. If it is cooled as it is compressed until it is under a great pressure and is at the ordinary temperature, and is then relieved of its pressure, it expands again and its temperature falls far below the surroundings.

[illegible] in which the expansion is [illegible]

[illegible] is a good solvent for the *ethereal* oils [illegible] in extracting the odors from flowers. [illegible] makes it possible to separate [illegible] the extracted odorous substances, which [illegible] volatile.

Methyl chloride may also be called *chlormethane*. [illegible] gives an idea of the nature of the [illegible] substance it is derived.

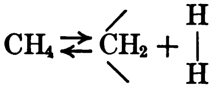
[illegible] methyl chloride behaves very differently from [illegible] the halides of the metals. The latter [illegible] a precipitate of silver halide. Methyl chloride gives a precipitate of silver chloride only [illegible] long in contact with silver nitrate in solution.

This difference in behavior is due to the fact that in solutions of the metallic halides the chlorine is *dissociated* from the metal to a considerable extent as chlorine ion:

$$NaCl \rightleftharpoons Na^+ + Cl^-$$

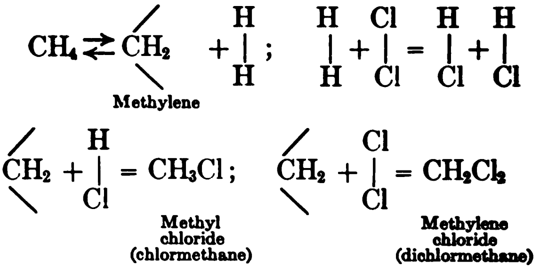
In the dissociated condition the chlorine ion carries a charge of negative electricity, and when a current of electricity is passed through a solution of sodium chloride the Na ion migrates to the negative pole and the Cl^- ion to the positive pole, thus transporting the charges which they carry. They are therefore conductors of electricity. Methyl chloride is not appreciably ionized when in solution, and does not therefore conduct the electric current. Its low order of reactivity with $AgNO_3$ is also the result of its nearly undissociated condition. In general molecules do not react with each other, but chemical change is usually the result of the property of compounds which causes them to dissociate into simpler parts which are in a much more active state chemically than the molecule from which they were formed. Since methyl chloride does react very slowly with $AgNO_3$ it is believed by many chemists to be in a very slight degree dissociated.

A compound such as CH_4, in which all the valences of each of the atoms it contains are saturated, should theoretically show no tendency to react with other chemical substances. The reason why, *e.g.*, chlorine does react with methane is best explained by the theory elaborated by Nef, which postulates a *very slight* dissociation of methane into methylene and hydrogen:



$$CH_4 \rightleftarrows \overset{/}{\underset{\backslash}{C}}H_2 + \begin{matrix} H \\ | \\ H \end{matrix}$$

These components are in dynamic equilibrium with each other. This means that any agent which removes one of the dissociation products will induce the further dissociation of a part of the CH_4 molecules to maintain certain relationships with respect to the three components of the system. Only the dissociation products are active chemically so that the speed of reaction will be determined by the degree of dissociation of the methane. This is greater at higher temperatures than at lower, so that reactions of this sort are greatly accelerated by heat. According to this theory the reaction of methane with chlorine takes place in the following way:



$$CH_4 \rightleftarrows \overset{/}{\underset{\backslash}{CH_2}} + \begin{matrix} H \\ | \\ H \end{matrix}\ ; \quad \begin{matrix} H \\ | \\ H \end{matrix} + \begin{matrix} Cl \\ | \\ Cl \end{matrix} = \begin{matrix} H \\ | \\ Cl \end{matrix} + \begin{matrix} H \\ | \\ Cl \end{matrix}$$

Methylene

$$\overset{/}{\underset{\backslash}{CH_2}} + \begin{matrix} H \\ | \\ Cl \end{matrix} = CH_3Cl\ ; \quad \overset{/}{\underset{\backslash}{CH_2}} + \begin{matrix} Cl \\ | \\ Cl \end{matrix} = CH_2Cl_2$$

Methyl chloride (chlormethane)

Methylene chloride (dichlormethane)

Simultaneously some of the active methylene groups should theoretically react with each other forming molecules with two carbon atoms, etc. This theory is in accord with the observed facts, viz. that the reaction of methane with chlorine does not lead to the formation of a single product, but of several products simultaneously. In representing the reactions between organic compounds among themselves and with inorganic substances, the equation written represents the principal reaction only. Further evidence in support of this belief will be presented later.

3. The Geometrical Structure of Methane. — The experience of many chemists has shown that the relationship which exists between the very numerous organic compounds can be expressed in a very useful way by assuming that the atoms which make up the molecules occupy definite relations to each other in space. The carbon atom is conceived to have its four affinities directed toward the angles of a regular four-sided figure (tetrahedron), the C atom itself occupying the center (Fig. 1).

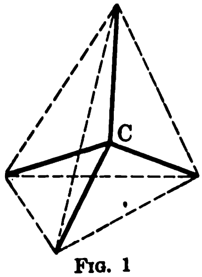


Fig. 1

Methane is expressed by the spatial formula shown in Figure 2, the hydrogen atoms forming a system of satellites about the C atom which may be likened to the sun and the planets of the solar system. Chlormethane or methyl chloride is represented by the structure in Figure 3.

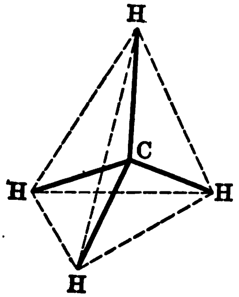


FIG. 2

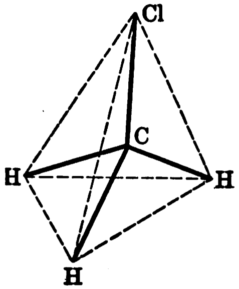
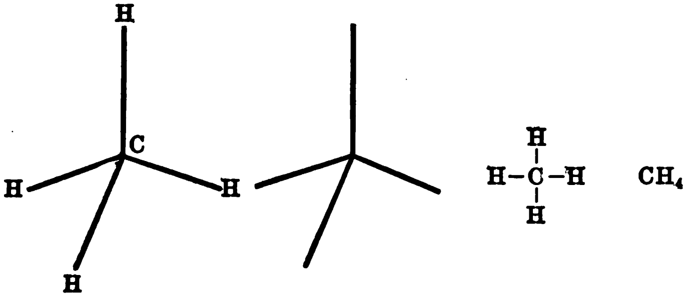


FIG. 3



(a) (b) (c) (d)

FIG. 4

This formula is, however, so cumbersome to write that in ordinary practice it is not employed. Figure 4 shows the various types of simplified figures employed to describe the carbon atom and its many derivatives produced by the substitution of its hydrogen atoms by other elements or complexes.

Of these symbols CH_4 is employed in all ordinary cases in writing formulæ. It is known as the *empirical formula,* the geometrical arrangement being employed only for special demonstration. The student should accustom himself to visualize the spatial formulæ.

Now in Figure 2 each of the four hydrogen atoms occupies the same relative position with respect to the C atom and it should make no difference whether, in making chlormethane, we substitute one hydrogen atom, or another, by the chlorine. The methyl chloride should have the same *configuration* in each case, which is equivalent to saying that only one methyl chloride is possible. This is in accord with experience. No matter how methyl chloride be prepared, and there are several methods for its preparation, the product always has the same specific gravity, boiling point, and other physical properties.

In assigning four valences to carbon, it should be borne in mind that there is one very common compound, carbon monoxide, CO, in which carbon must exist in the divalent state, or with two of its valences polarized or latent. In a number of its compounds carbon shows a marked tendency to pass from the tetravalent into the divalent state, or vice versa. This is seen in the relation between carbon dioxide and carbon monoxide (also called carbonic oxide). At ordinary temperatures CO_2 is a stable gas, but under the influence of the silent electrical discharge it tends to change into $CO + O$. Carbon monoxide on the other hand can readily add on certain elements, as chlorine, the carbon passing back into the tetravalent state.

$$\begin{aligned} CO + O &= CO_2 \\ CO + Cl_2 &= \underset{\substack{\text{Carbonyl}\\ \text{chloride}}}{COCl_2} \end{aligned}$$

The latter reaction takes place very slowly in the dark, but is greatly accelerated by sunlight. Most organic substances exhibit this tendency to pass in some degree into labile active forms.

4. If in a mixture of methane and chlorine the latter is present in excess two, three, or four hydrogen atoms are substituted by chlorine. These are called dichlor, trichlor, and tetrachlor methane, respectively. Since the group CH_2 is termed *methylene* (**2**), dichlormethane is sometimes called *methylene chloride.* Trichlormethane is *chloroform,* a familiar substance employed as an anesthetic. Tetrachlormethane is familiarly known as *carbon tetrachloride.* It is much employed as a solvent for fats and oils, and is used in the dry cleaning of clothes. Its action is to dissolve the grease from spots and when the latter is removed from the fabric the dirt which adhered to the grease readily separates. Both chloroform and carbon tetrachloride are non-inflammable.

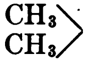
There are bromine and iodine substitution products of methane, entirely analogous to the chlorine compounds. Some of these are of great interest and value in synthetic work. While chlorine reacts with methane at ordinary temperatures, forming substitution products and hydrochloric acid, bromine must be heated in a sealed tube before any reaction will take place, and iodine will not react with methane, even under pressure and at high temperatures, to form substitution products.

5. Methyl Iodide. — For the preparation of the iodine derivatives advantage is taken of the greater affinity of the mono- and divalent metals for chlorine than has the methyl radical, thus:

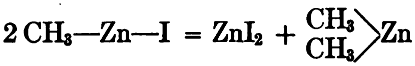
$$CH_3Cl + KI = \underset{\text{Methyl iodide}}{CH_3I} + KCl$$

Methyl iodide is a heavy liquid with a pleasant ethereal odor, boiling at 43° C. Its specific gravity is 2.19. It is so unstable that on keeping it decomposes, setting free iodine.

6. Ethane, C_2H_6.

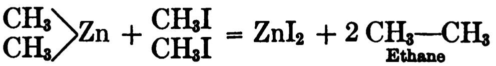
Zinc methyl:  $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>Zn$ is a derivative of methane which is formed when methyl iodide is warmed with a mixture of zinc and copper in a powdered form. The reaction may be represented as follows:

$$CH_3I + Zn = CH_3{-}Zn{-}I$$



$$2\,CH_3{-}Zn{-}I = ZnI_2 + \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>Zn$$

Zinc methyl is a colorless liquid boiling at 46° C., which is so unstable that it explodes when exposed to the oxygen of the air. It is therefore a highly reactive substance and can be used to build up synthetically other hydrocarbons from methane. Zinc methyl reacts readily with methyl iodide to form *ethane*:

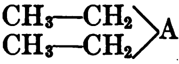


$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>Zn + \begin{matrix}CH_3I\\CH_3I\end{matrix} = ZnI_2 + 2\,\underset{\text{Ethane}}{CH_3{-}CH_3}$$

It can also be prepared by the reaction of Wurtz and Fittig, in which methyl iodide is allowed to react with metallic sodium:

$$2\,CH_3I + 2\,Na = CH_3—CH_3 + 2\,NaI$$

Certain metallic derivatives of methane and ethane are of biological importance. Animals poisoned with tellurium or selenium compounds eliminate in the breath dimethyl telluride $CH_3—Te—CH_3$ and dimethyl selenide $CH_3—Se—CH_3$ respectively. These possess characteristic odors, that of dimethyl telluride resembling garlic. The organism is thus capable of employing the methyl radical to combine with these toxic elements in order to produce volatile derivatives which can be eliminated.

Dimethyl telluride is a heavy yellow oil which boils at 82°. Dimethyl selenide is a liquid. When certain molds, especially *Penicillium brevicaule,* are grown upon media containing arsenic, they produce volatile *diethyl arsine,*  $\left.\begin{matrix}CH_3—CH_2\\CH_3—CH_2\end{matrix}\right>AsH$, which has a garlic-like odor. The test is so delicate that even 0.00001 gram of arsenic can be detected with certainty.

It is through the agency of such molds that poisoning with arsenic has resulted from the use of wall paper printed with arsenic-containing pigments.

From its method of formation ethane is therefore believed to be made up of a methane molecule in which one hydrogen atom is substituted by a methyl group. Its structure

NOTE. — Unless otherwise specified all temperatures refer to the Centigrade scale.

is assumed to be that shown in Figure 5 (*a*) and (*b*), but for simplicity the formulæ (*c*), (*d*), or (*e*) are employed.

Ethane may be regarded as methyl methane and is occasionally spoken of as dimethyl. It is a colorless and odorless gas which is liquefied at 4° by 46 atmospheres pressure. It is slightly more soluble than methane in water and alcohol. It occurs with methane in natural gas and is present in petroleum.

The property of the carbon atom of combining with other carbon atoms in a very firm union to form *carbon chains* is unique among the elements. Ethane and its *homologues* are very stable substances and very resistant to reagents.

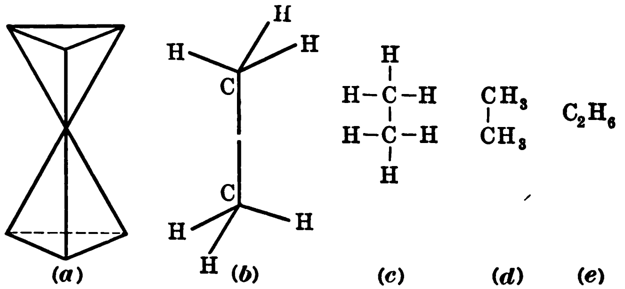


Fig. 5.

Ethyl chloride, $CH_3—CH_2Cl$, can be prepared by the action of chlorine on ethane:

$$CH_3—CH_3 + 2Cl = CH_3—CH_2Cl + HCl$$

The ethane molecule less one hydrogen atom is called the *ethyl radical* or group. Methyl, ethyl, and their higher homologues are frequently called alkyl radicals or groups, and their halogen derivatives *alkyl halides*.

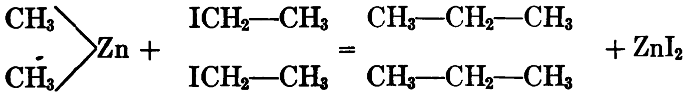
Ethyl chloride is a sweet-smelling liquid boiling at 12.5°. In a manner entirely analogous to the formation of methyl iodide, ethyl iodide can be produced from the chloride:

$$CH_3—CH_2Cl + KI = \underset{\text{Ethyl iodide}}{CH_3—CH_2I} + KCl$$

Ethyl iodide boils at 72°. It can react with methyl iodide to produce a hydrocarbon containing three carbon atoms, called *propane*:

$$CH_3—CH_2I + CH_3I + 2\,Na = \underset{\text{Propane}}{CH_3—CH_2—CH_3} + 2\,NaI$$

This synthesis can also be effected by the action of zinc methyl on ethyl iodide:



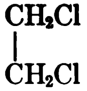
$$\left.\begin{array}{l}CH_3\\CH_3\end{array}\right\rangle Zn + \begin{array}{l}ICH_2—CH_3\\ICH_2—CH_3\end{array} = \begin{array}{l}CH_3—CH_2—CH_3\\CH_3—CH_2—CH_3\end{array} + ZnI_2$$

If metallic sodium be allowed to act on ethyl iodide, two ethyl radicals are combined to form butane:

$$CH_3—CH_2I + ICH_2—CH_3 = \underset{\text{Butane}}{CH_3—CH_2—CH_2—CH_3}$$

Since it will be necessary later to speak of the dihalogen derivatives of ethane in illustrating the structure of certain compounds (aldehydes), mention should here be made of the nomenclature of these.

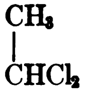
When two of the hydrogen atoms of ethane are replaced by halogen, two compounds are possible according to whether the halogen atoms are attached to the same or to different carbon atoms.



$$\begin{array}{l} CH_2Cl \\ | \\ CH_2Cl \end{array}$$

Ethylene chloride

and



$$\begin{array}{l} CH_3 \\ | \\ CHCl_2 \end{array}$$

Ethylidene chloride

The *symmetrical* isomer is distinguished by the ending *ene* and the unsymmetrical isomer by the ending *idene* preceded by the prefix denoting the hydrocarbon from which it was derived. Compounds of this class will be considered later (**31**).

7. Starting with methane, therefore, it is possible to build up a series of hydrocarbons each differing from the next lower one by a CH_2 group. Their formulae, CH_4, C_2H_6, C_3H_8, C_4H_{10}, C_5H_{12}, C_6H_{14}, etc., all correspond to the general expression C_nH_{2n+2}. They have the general name of *saturated hydrocarbons,* because all the valences of the carbon atoms not holding other carbon atoms are saturated with hydrogen, so that they cannot take up any more of the latter.

Nomenclature. — The saturated hydrocarbons are designated by the termination "ane." Methane, ethane, propane, and butane, have special names. The higher ones are denoted by the Greek or Latin numeral signifying the number of carbon atoms they contain. Thus, C_6H_{14} is called hexane; $C_{10}H_{22}$, decane; $C_{16}H_{34}$, hexadecane; etc.

The groups of atoms which are derived from the hydrocarbons by the removal of a hydrogen atom are termed *alkyl groups*; they are denoted by changing the ending "ane" to "yl." Thus CH_3—, is methyl; C_2H_5—, ethyl; C_3H_7—, propyl; C_4H_9—, butyl; etc.

Properties of the paraffins. The compounds of this series containing from 1 to 4 carbon atoms are gases; those with 5 to 16 carbon atoms, liquids at ordinary temperatures and pressures; while those having more than 16 carbon atoms in the molecule are solids. Members containing from 1 to 60 carbon atoms are actually known.

8. Crude Petroleum, which occurs in nature in enormous quantities, consists of a mixture of all the members of the series from the lowest to the highest. When distilled the lower members volatilize first, the temperature in the still rising as the distillation proceeds. The lightest fraction which is collected distills at 0° and consists of gases, chiefly butane, which are liquefied under pressure and employed for the production of low temperatures. As a rule the distillate is collected until the product coming over has a specific gravity of .729. This is reached at a temperature of about 150°, at which point chiefly nonane and decane distill. All the product so obtained is known as *crude naphtha.* This is redistilled and separated into *rhigolene* B. P. 18°, *petroleum ether* or *naphtha* B. P. 50–60, containing chiefly C_5H_{12} and C_6H_{14}; benzine B. P. 70–90°, chiefly C_6H_{14} and C_7H_{16}; ligroin B. P. 90–120°, and petroleum benzine B. P. 120–150°, chiefly mixtures of C_7H_{16} and C_8H_{18}. From 150–300° there is collected the "burning oil distillate," which is redistilled into several grades of *kerosene.* The safety of these oils depends on their volatility, for their vapors mixed with air form explosive mixtures. Their use is attended with considerable danger. The quality of the product is determined by the *flash point* and "burning point." These are determined by heating a sample in a dish and at intervals bringing a small flame near the surface. When vapors are given off rapidly enough to form a combustible mixture, there is a flash, which is at once extinguished. At a higher temperature vapors are given off rapidly enough to support a flame. This is known as the burning point. Most states require a flash point of at least 110° F. and a burning point of 110 to 150° F.

Above 300° F. there are distilled various grades of lubricating oils. From the residues vaseline and paraffin are separated, the latter by chilling.

The physical constants of a number of the normal hydrocarbons are given below:

TABLE I

		MELTING POINT	BOILING POINT		SPECIFIC GRAVITY	
CH_4	Methane	− 184°	− 164°		.415	at 16.4°
C_2H_6	Ethane	− 172.1	− 84.1		.446	40°
C_3H_8	Propane	− 45	− 44.5		.535	
C_4H_{10}	Butane	—	− 1		.600	
C_5H_{12}	Pentane	—	36.3		.454	
C_6H_{14}	Hexane	—	69		.660	at 20°
C_7H_{16}	Heptane	—	98.3		.683	
C_8H_{18}	Octane	—	125.8		.702	
$\vdots$						
$C_{16}H_{34}$	Hexadecane	18	287		.775	At the M. P.
$C_{17}H_{36}$	Heptadecane	22	303		.777	
$C_{18}H_{38}$	Octadecane	28	317		.777	
$\vdots$						
$C_{27}H_{56}$	Heptacosane	60	270	At 15 mm. pressure	.780	
$C_{31}H_{64}$	Hentriacontane	68	302		.781	
$C_{32}H_{66}$	Dotriacontane	70	310		.781	
$C_{35}H_{72}$	Pentatriacontane	75	331		.782	

9. Isomerism. — Just as in the case of methane, there is but one substance known having the formula CH_4, so there is but one compound having the formula C_2H_6 (ethane), and one having the formula C_3H_8 (propane). Butane, C_4H_{10}, however, exists in two forms. They have the same percentage composition with respect to carbon and hydrogen, and the same molecular weight, but differ in their boiling points and specific gravities. Both are gases, but one is liquefied at – 1° while the other remains a gas until cooled to – 17°. The existence of two or more compounds having the same chemical formula but different physical properties is explained by the structural formulas. Thus while all the hydrogen atoms in methane and ethane are alike with respect to the remainder of the molecule; in propane and butane and the higher homologues this is not the case, as is illustrated in Figure 6.

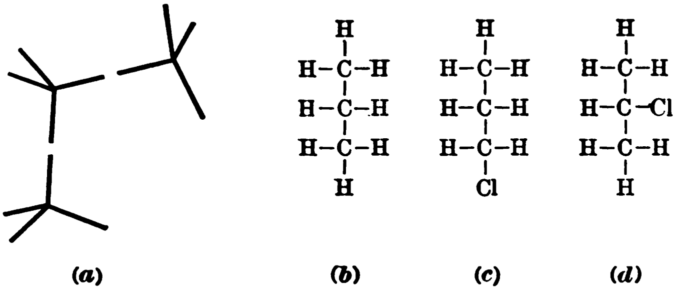
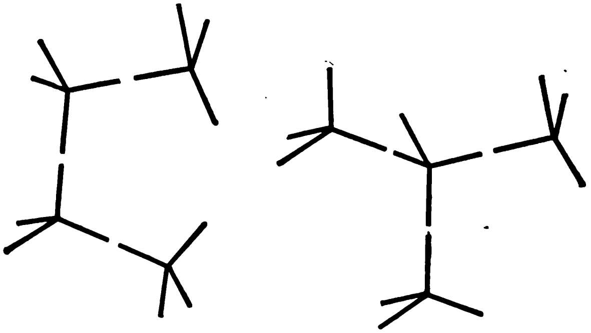
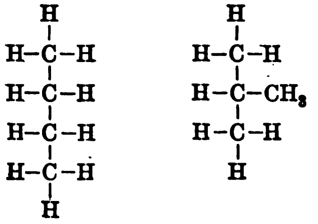


FIG. 6.

If in (*b*) a chlorine atom should be substituted for a hydrogen atom, the same chlor propane or *propyl chloride* should result whichever one of the hydrogen atoms attached to either end carbon atom might be replaced, but a different compound should result provided the chlorine should be substituted for a hydrogen attached to the middle carbon atom.. This C atom differs from the two end ones in that two of its valences are in union with



Normal butane Isobutane



Normal butane (methyl-ethyl-methane) Isobutane (trimethyl methane)

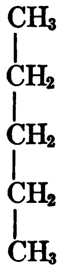
FIG. 7.

methyl groups, while the others are each linked to carbon by only one bond. Theory calls therefore for only one propane, and only one is known, while it calls for two mono-chlor propanes and both of these are known. *Normal* propyl chloride, $CH_3—CH_2—CH_2Cl$, abbreviated *n*-propyl chloride, boils at 46.4°, while *iso*propyl chloride, $CH_3—CHCl—CH_3$, boils at 36.5°.

We should expect in the case of butane two forms corresponding to the propyl chlorides, the methyl group occupying the position of the chlorine atoms (Fig. 7).

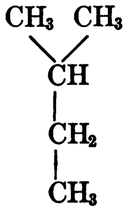
Isobutane consists of a *branched chain* of carbon atoms, normal butane does not. Such a difference in structure is called *isomerism* and the compounds so related are *isomers.* Normal butane may be looked upon as methyl-ethyl-methane, since two hydrogens are respectively substituted by a methyl and an ethyl radical.

Three pentanes should exist if our theory of structure is correct and as a matter of fact three are known:

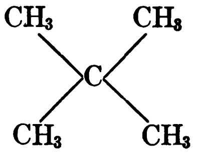


$$\begin{matrix} CH_3 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ CH_3 \end{matrix}$$

n-pentane (methyl-propyl-methane)



Dimethyl-ethyl-methane



Tetramethyl-methane

The boiling points of the normal hydrocarbons are always higher than those of the isomers, and the boiling point becomes continuously lowered the more the carbon chain is branched, *i.e.* the more the methyl groups are gathered together in the molecule.

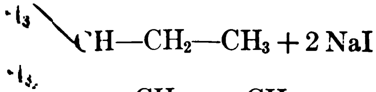
The constitution of the hydrocarbons of the paraffin series can be arrived at only by their synthetical formation

ructure. Thus, by the
normal propyl iodide and
one molecule of normal
propyl iodide and one of
i-ethyl-methane (2); and
dies and methyl iodide are
ane (3):

$-CH_3 + 2\,Na$

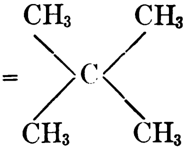
$CH_2-CH_2-CH_3 + 2\,NaI$

$CH_3 + 2\,Na$



$\begin{matrix} CH_3 \\ CH_3 \end{matrix} > CH-CH_2-CH_3 + 2\,NaI$

$2\,Na =$



$C(CH_3)_4$

increases very rapidly
The following table shows
for some of them:

Decane	$C_{10}H_{22}$	75
Undecane	$C_{11}H_{24}$	159
Dodecane	$C_{12}H_{26}$	354
Tridecane	$C_{13}H_{28}$	802

35

Most of the higher ones have never been prepared because they are not of sufficient importance to induce chemists to give the necessary effort. The methods of forming them are well understood and it is quite possible to produce large numbers of them synthetically.

10. A carbon atom which is only linked to one other carbon atom is called *primary*; one which is linked to two carbon atoms is *secondary*; one linked to three is *tertiary*; and to four, *quaternary*. When situated at the end of a chain a carbon atom is called *terminal*. The carbon atoms of a chain are designated by numbers, the terminal one being denoted by 1, the next by 2, etc., for example:

$$\underset{1}{CH_3}—\underset{2}{CH_2}—\underset{3}{CH_2}—\underset{4}{CH_2}—\underset{5}{CH_2}\cdots$$

Frequently the longer chains are written

$$CH_3—(CH_2)_n—CH_3.$$

The terminal carbon atom is frequently denoted by ω, the Greek letter *omega*, the next by α (*alpha*) and the succeeding ones by β, γ, etc. Methane and its homologues are collectively spoken of as the *methane series*, or the *paraffin hydrocarbons*.

11. The assumption that the four valences of the carbon atom are directed toward the angles of a regular tetrahedron does not necessitate regarding their positions with respect to each other as fixed. There is good reason to believe that they may revolve around a position of equilibrium without changing the order of succession.

CHAPTER II

THE ALCOHOLS

12. The Monatomic Alcohols.—When methyl chloride, bromide, or iodide is warmed with water, halogen acid and a new substance, methyl alcohol, are formed. It may be looked upon as water in which one H atom is replaced by the CH_3 radical.

$$CH_3Cl + HOH = \underset{\text{Methyl alcohol}}{CH_3OH} + HCl$$

Its synthetic formation has only a scientific interest, for in practice it is always obtained as a by-product of wood distillation.

The alcohols and the corresponding alkyl halides are in general mutually transformable into each other. Thus on treatment with phosphorus pentachloride the alcohols are converted into alkyl chlorides, the OH group being replaced by Cl:

$$CH_3—CH_2OH + PCl_5 = CH_3—CH_2Cl + \underset{\text{Phosphorus oxychloride}}{POCl_3} + HCl$$

It is customary in illustrating reactions which, like this one, are characteristic of a series by employing the symbol R in place of the alkyl group attached to carbinol, as:

$$R—CH_2OH + PCl_5 = R—CH_2Cl + POCl_3 + HCl$$

Methyl alcohol is known as wood alcohol because it is produced when wood is heated out of contact with the oxygen of the air to a temperature sufficient to decompose it.

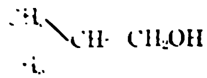
Properties. The methyl alcohol of commerce is obtained in this way. It is a colorless liquid which is neutral in reaction; that is, it does not dissociate H^+ or OH^- ions, a fact which is shown by its failure to act on indicators such as litmus, or to conduct the electric current. It is soluble in water in all proportions, has a burning taste, and boils at 64.5°.

Methyl alcohol is the lowest member of a homologous series of alcohols derived from the hydrocarbons of the methane series, the second member being *ethyl alcohol* $CH_3—CH_2OH$.

13. Nomenclature of the Alcohols. — Certain of the more common alcohols have received special names which they retain as the result of long usage. In the systematic nomenclature usually employed they are regarded as derivatives of *carbinol* or methyl alcohol. This system is of especial utility in indicating the structures of the isomeric alcohols. Thus ethyl alcohol is *methyl carbinol,* CH_3CH_2OH, and the two primary butyl alcohols are *propyl carbinol* and *isopropyl carbinol.* Further examples are given in connection with the amyl alcohols (**20**).

Another system of nomenclature which is frequently employed is that of using the name of the hydrocarbon with the same number of carbon atoms and employing the suffix -ol to indicate the alcohol. Thus methyl alcohol is methanol; ethyl alcohol, ethanol; etc.

ship of the first five alcohols to the cor-
responding carbinols is illustrated by the following

CH_3OH	Methanol, carbinol.
$CH_3 \cdot CH_2OH$	Ethanol, methyl carbinol.
$CH_3 \cdot CH_2 \cdot CH_2OH$	Propanol, ethyl carbinol.
$CH_3 \cdot (CH_2)_2CH_2OH$	Butanol, n-Propyl carbinol.
 $CH_3 \backslash CH \cdot CH_2OH$	Isobutanol, Isopropyl carbinol.
$CH_3 \cdot (CH_2)_3 \cdot CH_2OH$	*n*-Pentanol, *n*-Butyl carbinol.

alcohol, *ethanol, methyl carbinol.*—This is
obtained by fermentation of sugar by
all fermented liquids such as wine
made chiefly from potatoes, grains,
starch is converted into sugar and
and carbon dioxide. The chemical
this process will be described in con-
tation of sugars (**164**).
pared technically by distilling fer-
is a liquid of agreeable odor,
although the fermented liquids
18% of alcohol, by carrying
fractionating column alcohol of
be obtained. The fractionating
which a relatively large cooling
considerable time is allowed for
less volatile liquid. There are

ordinarily placed in the vapors ascending from the still, obstructions such as glass beads or platinum gauze, to retard their escape, thus giving greater opportunity for the condensation of the higher boiling liquid of the mixture, which then runs back into the still. The lower boiling constituent escapes condensation and passes over into the receiver.

On redistilling the alcohol thus obtained in an efficient rectifying apparatus a product containing but 4% of water is obtained. This strength of alcohol is much used in the arts as a solvent.

Absolute alcohol is obtained by treating 96 % alcohol with quicklime, which removes the water, forming calcium hydrate, $Ca(OH)_2$. The alcohol is then rectified again. The product so obtained contains about .5 % of water. This is the commercial absolute alcohol. Pure absolute alcohol is obtained by treating the latter with a small amount of metallic sodium or calcium and distilling again. Traces of water in alcohol can be readily detected by placing in it a small amount of copper sulphate from which the water of crystallization has been driven off by heating. This is a white powder. The anhydrous $CuSO_4$ takes up even very slight traces of water from the alcohol and forms the deep blue hydrated salt.

Among inorganic substances alcohol dissolves the halogens, sulphur and phosphorus to some extent, boracic acid, the hydrates of potassium and sodium, the chlorides of calcium and strontium, ferric chloride and mercuric chloride. It is also a solvent for many organic acids, bases, and neutral substances, the resins, soaps, and fats. Alco-

[illegible] employed in medicine are [illegible] tures. Certain proteins of [illegible] in 70 % alcohol, but most [illegible] their solutions by alcohol.

[illegible] now sold without the pay- [illegible] tax which is levied on all [illegible] alcohol to be tax free must be [illegible] for drinking by the addition [illegible] substances. The regulations [illegible] issioner of Internal Revenue [illegible] parts of methyl alcohol and 1 [illegible] parts of alcohol. Another [illegible] requires the addition of 2 parts [illegible] parts of pyridine.

[illegible] distributed in nature. Small [illegible] in the distillate from leaves, [illegible] in humus-rich soil. Traces [illegible] yeast. Very small amounts [illegible] blood and tissues of animals. [illegible] reasons for believing that in the [illegible] through the normal physiological [illegible] an intermediate product.

[illegible] Metallic sodium reacts with [illegible] forming sodium ethylate and

[illegible] $Na = C_2H_5ONa + H$

[illegible] readily soluble in alcohol and forms [illegible] compound, $C_2H_5ONa + 2C_2H_5OH$. This [illegible] the sodium ethylate as [illegible] useful in synthetic work.

Potassium acts violently on alcohol, forming potassium ethylate.

16. Alcoholic Beverages. — There are two classes of alcoholic beverages in use: those which are the direct product of fermentation by yeast; and those which are prepared by distilling the fermented liquid, as molasses or extracts, prepared by conversion of the starches of certain grains, potatoes, etc., into sugar, and dissolving out the latter. The undistilled beverages contain much less alcohol than the distilled.

Beer is prepared by fermenting malted (*i.e.* sprouted) grains. It contains 3 to 5 per cent of alcohol and derives its bitter taste from the addition of an infusion of hops.

Wine and *champagne* are fermented fruit juices, principally grape juice. As fermented, a beverage never contains more than about 15 to 18 per cent of alcohol, but wines are frequently " fortified " by the addition of alcohol to a content of 20 %.

Whiskey is prepared by the fermentation of malted grains. After the fermentation by yeast is completed, the product is distilled and the distillate condensed. Ordinarily it is twice distilled and water is added to the distillate to make a solution containing about 50 to 58 % of alcohol by volume.

Brandy is made by distilling wines or fermented peach, apple, or other juices. Its alcohol content varies from 44 to 55 %.

Gin is whiskey which has been distilled with aromatic substances such as juniper berries, anise seed, etc., which give it its peculiar flavor.

Rum is made from fermented molasses. It not infrequently contains enough of the higher alcohols, butyl and amyl alcohols and their esters, to render it more toxic than ordinary whiskey prepared from grains.

17. Higher Homologues of Ethyl Alcohol. —

CH_4 Methane

$CH_3—CH_3$ Ethane

$CH_3—CH_2—CH_3$ Propane

$CH_3—OH$ Methyl alcohol

$CH_3—CH_2OH$ Ethyl alcohol

$CH_3—CH_2—CH_2OH$ Propyl alcohol

$CH_3—(CH_2)_2—CH_3$ Butane

$CH_3—(CH_2)_3—CH_3$ Pentane

$CH_3—(CH_2)_2—CH_2OH$ Butyl alcohol

$CH_3—(CH_2)_3—CH_2OH$ Amyl alcohol

Being derived from the hydrocarbons of the C_nH_{2n+2} series by the replacement of H by OH these alcohols have the general formula $C_nH_{2n+1}OH$. Those derived from the normal hydrocarbons are normal alcohols. If the OH group is attached to an end carbon atom it is known as a *primary;* if to a secondary carbon atom, a secondary; and if to a tertiary carbon atom, a tertiary alcohol. Those derived from branched chain hydrocarbons are *iso* alcohols, and may be primary or secondary:

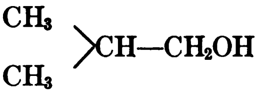
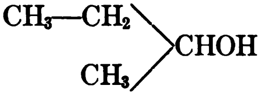
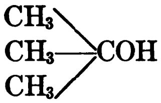
$CH_3—CH_2—CH_2OH$ Primary propyl alcohol (normal)

$CH_3—CH(OH)—CH_3$ Secondary propyl alcohol (isopropyl alcohol)

18. The Butyl Alcohols. — C_4H_9OH.

	BOILING POINT	SPECIFIC GRAVITY AT 20°
1. $CH_3—CH_2—CH_2—CH_2OH$	117°	.810

Normal butyl alcohol (primary)
(Propyl carbinol)

2.	 Isobutyl alcohol (primary) (Isopropyl carbinol)	107°	.806
3.	 Normal secondary butyl alcohol (Methyl ethyl carbinol)	100°	.808
4.	 Tertiary butyl alcohol (Trimethyl carbinol)	83°	.786

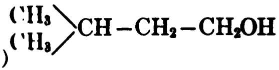
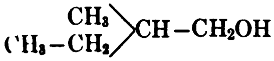
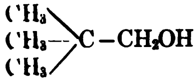
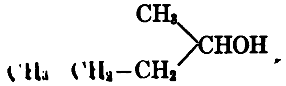
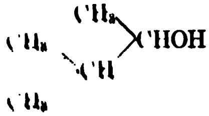
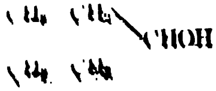
Normal primary butyl alcohol occurs in fusel oil to a small extent, but has little biological importance. It is produced, together with a number of other products, by *Bacillus butylicus*, growing on glycerin and various sugars and related substances (see butyric acid fermentation, **164**).

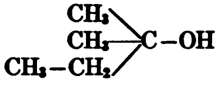
The most important butyl alcohol is *isopropyl* carbinol. It is produced by yeasts during fermentation of sugar into ethyl alcohol and carbon dioxide. It has its origin not from sugar, but from one of the protein digestion products, valin. It is formed in relatively large amounts when potatoes are malted and fermented by yeasts, because the mother substance valin (**73**) is present in greater amount than in the malted grains.

The remaining two butyl alcohols have been prepared synthetically, but do not occur in nature.

Physiological properties. — The butyl alcohols are all distinctly poisonous both to plants and animals. The toxic action of monatomic alcohols increases with higher carbon content and with increasing molecular weight. This is the *Rule of Richardson.* The normal primary alcohol is more toxic than isopropyl carbinol, and the latter is more toxic than secondary and tertiary butyl alcohols.

19. The Amyl Alcohols. —

		Boiling Point	Specific Gravity at 20°
1. Normal primary (butyl carbinol)	$CH_3-CH_2-CH_2-CH_2-CH_2OH$	138°	.817
2. Isobutyl carbinol (primary) (Active amyl alcohol)	 $\begin{matrix}CH_3\\CH_3\end{matrix}>CH-CH_2-CH_2OH$	130°	.810
3. Secondary butyl carbinol (primary)	 $\begin{matrix}CH_3\\CH_3-CH_2\end{matrix}>CH-CH_2OH$	128°	.816
4. Tertiary butyl carbinol (primary)	 $\begin{matrix}CH_3\\CH_3\\CH_3\end{matrix}>C-CH_2OH$	113°	—
5. Methyl propyl carbinol (secondary)	 $\begin{matrix}CH_3\\CH_3\;\;CH_2-CH_2\end{matrix}>CHOH$	119°	—
6. Methyl isopropyl carbinol (secondary)	 $\begin{matrix}CH_3\\CH_3\;\;CH\\CH_3\end{matrix}>CHOH$	112°	.819
7. [illegible]	 $\begin{matrix}CH_3\;\;CH_2\\CH_3\;\;CH_2\end{matrix}>CHOH$	117°	—

8. Dimethyl ethyl carbinol (tertiary)	 $(CH_3)_2(CH_3{-}CH_2)C{-}OH$	102°	—

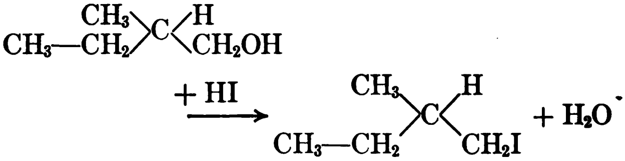
The only two amyl alcohols which are of any great importance in biological processes are *primary isobutyl carbinol* and *secondary butyl carbinol.* These both occur in fusel oil through the life processes of yeasts, and, like isobutyl alcohol, are derived from the cleavage products of proteins (**75**).

Physiological Properties. — All have disagreeable smells and produce headache. Normal amyl alcohol is about four times as toxic as ethyl alcohol. A .5 % solution quickly destroys infusoria, and a 1 % solution kills algæ within a day. In dilutions as great as .1 % certain bacteria can use it as a source of carbon.

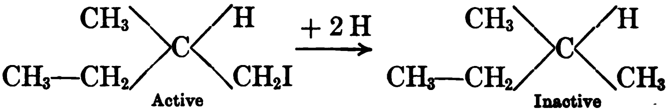
A saturated (2.5 %) solution of isoamyl alcohol exerts a powerful bactericidal action. The toxicity of the amyl alcohols is distinctly greater than that of the lower members of the series. A $\frac{1}{10}n$ solution is as destructive to *B. pyogenes* as a $\frac{3}{10}n$ solution of butyl, a $\frac{5}{10}n$ solution of propyl, a $1\frac{3}{10}n$ solution of ethyl, and a $2\frac{1}{2}n$ solution of methyl alcohol.

20. Isomerism of the Amyl Alcohols. — One of the amyl alcohols, secondary butyl carbinol, also called active or fermentation amyl alcohol, presents a very interesting case of isomerism. Three isomers of this one alcohol are known, but they have all the same chemical and, with a single exception, the same physical properties. This exception is found in their action on polarized light. The ray of polarized light may be likened to a ribbon of light, as contrasted with a ray of ordinary light the waves of which are vibrating in every direction at right angles to the path of the ray. In the polarized ray the vibrations all lie in the same plane. When such a ray is passed into either of two of these amyl alcohols the ray is rotated by one of them to the right and by the other to the left. One is said to be dextrorotatory, the other levorotatory. The third produces no rotation at all. Two are said to be *optically active;* the other, *inactive.* The effect is as if the ray had received a twist in passing through the optically active substance.

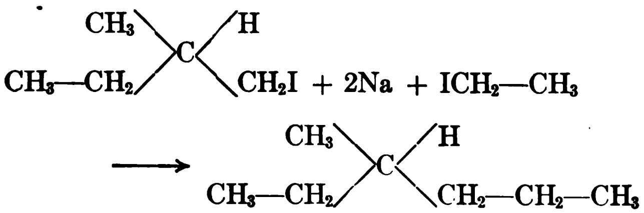
Now these two active isomers when treated with gaseous HI are transformed into two optically active amyl iodides, and the inactive one into an amyl iodide which is not optically active.



The amyl iodides, like the alcohols from which they were derived, have identical chemical and, except in their behavior toward polarized light, the same physical properties. Suppose we consider the iodide which is derived from *levorotatory amyl alcohol,* which is the important one from the biological standpoint. If it be converted into *pentane* by the action of nascent hydrogen, which removes the iodine, replacing it by H, there results a pentane which is *optically inactive:*

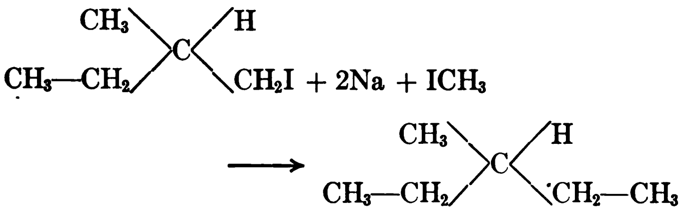


On the other hand, if this iodide is caused to react with ethyl iodide in the presence of sodium, there is produced a *heptane* which is optically active:



Methyl-ethyl-propyl-methane
(Active)

If the above reaction is carried out with methyl iodide instead of ethyl iodide there is formed a *hexane* which is optically inactive:



Methyl-diethyl-methane
(Inactive)

An inspection of these formulas shows that those compounds are optically active in which each of the bonds of affinity of one carbon atom is linked to different groups or atoms. Whenever two bonds of this carbon atom are linked to the same kind of group (as two methyl or two ethyl groups) the optical activity is lost.

Van't Hoff first discovered that optically active compounds have in general at least one carbon atom which is linked to four different atoms or radicals. He gave the name " asymmetric " carbon atom to one so linked.

Van't Hoff further showed that the existence of three isomers must necessarily result from the structure of an asymmetric carbon atom, if the assumption be correct that the four valences of the carbon atom are directed as toward the four solid angles of a regular tetrahedron, the carbon atom itself occupying the center of the figure.

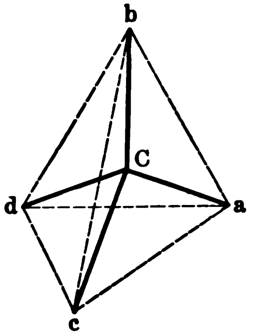


Fig. 8.

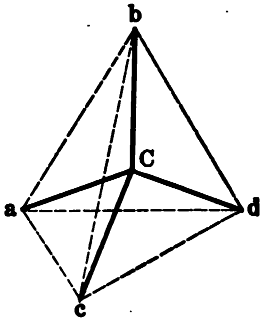
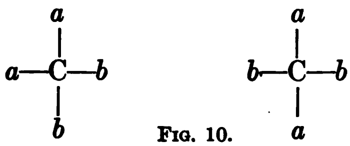


Fig. 9.

With such an arrangement there must result two kinds of molecules which resemble each other in the same way as the right hand resembles the left, or as an object resembles its reflection in a mirror. If such molecules be represented as mirror images (Fig. 8 and Fig. 9) it will be seen that on turning one so that the *a* and *b* in both figures coincide, the *c* and *d* of one will not coincide with *c* and *d* of the other. If now Figure 8 rotates the plane of polarized light to the right, Figure 9 will rotate it to the left because of its opposite handed structure. This isomerism in space is termed *stereochemical isomerism* or *stereoisomerism.*

For simplicity the formulæ of asymmetric compounds are written as if all the atoms or groups lie in the same plane. The belief that the atoms and groups in the compounds under discussion do not lie in the same plane is supported by the fact that compounds containing but two dissimilar groups, as C $aabb$, do not exist in two isomeric forms. If all were in the same plane two arrangements, like Figure 10, would be possible, which must lead to different physical properties because in the one case like groups are separated by unlike ones, while in the other like groups are adjacent to one another. No isomers of this type have ever been observed, although there are known a large number of compounds of the general formula Ca_2b_2.



$$\begin{array}{ccc} & a & \\ & | & \\ a\text{—} & \mathrm{C} & \text{—}b \\ & | & \\ & b & \end{array} \qquad \begin{array}{ccc} & a & \\ & | & \\ b\text{—} & \mathrm{C} & \text{—}b \\ & | & \\ & a & \end{array}$$

FIG. 10.

The third isomer of this amyl alcohol is a mixture of equal numbers of molecules of the right-and left-handed varieties. The influence of one-half of the molecules in rotating the plane of polarized light in one direction is exactly counteracted by the opposite rotating power of the other half, with the result that it appears to be without optical activity. When an excess of one optical form exists in a mixture of the two optically active varieties, this part exerts its effect and the mixture becomes optically active in proportion to the excess of one variety over the other.

This type of isomerism is of great significance in biology, since with but few exceptions the organic compounds which play important rôles in the life processes of plants and animals possess this type of asymmetry.

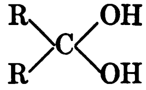
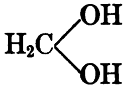
21. The Higher Alcohols. — One of the higher homologues of methyl alcohol which should be mentioned, is normal *hexyl* alcohol, $CH_3—(CH_2)_4—CH_2OH$ (B. P. 157°) which occurs in the oil of the seeds of *Heracleum giganteum,* in the oil of the fruit of several plants, and in slight amount in fusel oil. The following are also biologically important:

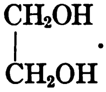
Normal heptyl alcohol	$CH_3—(CH_2)_5—CH_2OH$	B. P. 176°
Normal octyl alcohol	$CH_3—(CH_2)_6—CH_2OH$	B. P. 196°
Nonyl alcohol	$CH_3—(CH_2)_7—CH_2OH$	B. P. 213°
Dodecyl alcohol	$CH_3—(CH_2)_{10}—CH_2OH$	M. P. 24–26°
Cetyl alcohol	$CH_3—(CH_2)_{14}—CH_2OH$	M. P. 49°
Octadecyl alcohol	$CH_3—(CH_2)_{16}—CH_2OH$	M. P. 59°
Carnaubyl alcohol	$CH_3—(CH_2)_{22}—CH_2OH$	M. P. 68°
Ceryl alcohol	$C_{26}H_{53}OH$	
Myricyl alcohol	$C_{30}H_{61}OH$	

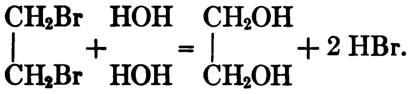
The higher alcohols, C_8 to C_{18}, are found in various plant oils in small amounts usually combined with organic acids, as esters (**28**). Cetyl alcohol occurs as a constituent of spermaceti, an animal wax derived from the sperm whale, and in the oil secreted by water birds for lubricating their feathers.

Ceryl alcohol is an important constitutent of many waxes, as Chinese wax, beeswax, etc.

Myricyl alcohol is likewise a very common constituent of waxes. (See waxes, **95**.)

22. The Diatomic Alcohols. — It has been found impossible to prepare in the isolated state compounds of the type  $R_2C(OH)_2$ such as  $H_2C(OH)_2$ for the reason that they are unstable and as soon as formed they separate a molecule of water with the formation of a new class of compounds, the aldehydes. These will be treated more fully later (**30**).

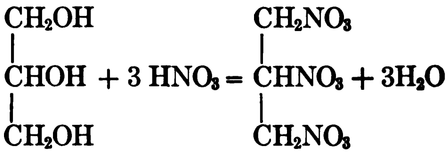
There are, however, many examples of compounds which contain more than one alcohol radical. The simplest of these is *ethylene glycol* or *glycol*  $\begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array}$ · It is formed in a manner analogous to monatomic alcohols, viz., by the action of water or metallic hydroxides on ethylene halogen derivatives (**6**). Ethylene chloride is too stable to react with water directly even under pressure, but ethylene bromide will react when heated in a sealed tube with water, forming glycol and hydrobromic acid:



$$\begin{array}{l} CH_2Br \\ | \\ CH_2Br \end{array} + \begin{array}{l} HOH \\ \\ HOH \end{array} = \begin{array}{l} CH_2OH \\ | \\ CH_2OH \end{array} + 2\,HBr.$$

Glycol is a colorless liquid, readily soluble in water, and has a sweet taste. It boils without decomposition at 197° and solidifies in a freezing mixture. Its melting point is − 11.5° and its specific gravity at 0° is 1.125, water being 1.000. It is therefore heavier, volume for volume, than any of the monatomic alcohols, which are all lighter than water.

long standing at low temperatures it solidifies, and the crystals thus formed do not melt below 17°. It boils at 290° but undergoes some decomposition. Under reduced pressure it can be distilled without decomposition. At 12 mm. it distills at 170°. It is slowly volatile with water vapor. Its specific gravity at 15° is 1.265. Its chemical behavior is in accord with the theory that it is a triatomic alcohol. Thus when glycerol is slowly dropped into a mixture of concentrated sulphuric acid and fuming nitric acid trinitroglycerol, usually called *nitroglycerine*, is formed. The sulphuric acid facilitates the reaction by its affinity for water, which it withdraws from the system as soon as formed:

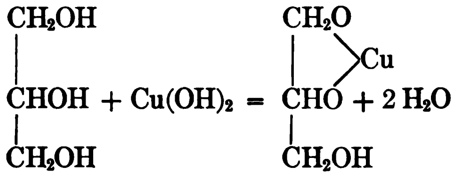


$$\begin{array}{llll} CH_2OH & & CH_2NO_3 & \\ | & & | & \\ CHOH & + 3\,HNO_3 = & CHNO_3 & + 3H_2O \\ | & & | & \\ CH_2OH & & CH_2NO_3 & \end{array}$$

Nitroglycerine

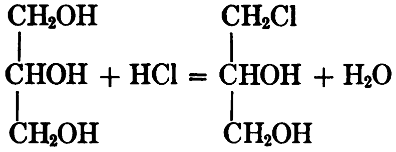
Nitroglycerine is a heavy colorless oil when pure, but usually has a yellow color. It is sweet to the taste and is extremely poisonous, acting chiefly on the central nervous system. It is employed in medicine for its action on the heart and is directly injected into the blood as a remedy in case of carbon monoxide poisoning. When heated to 180° it explodes. Its explosion can be induced by a sharp blow. The principal use of nitroglycerine is as an explosive. When absorbed by certain porous substances, as sawdust, clay, wood pulp, etc., it forms dynamite. Mixed with nitrocellulose, vaseline, and acetone, it forms the smokeless powder called *cordite*.

Glycerol, like other compounds containing several hydroxyl groups, dissolves alkalies and oxides of the heavy metals, forming compounds analogous to the alcoholates. The hydrogen atoms of the OH groups are in these replaced by the metal. The structure of such compounds may be illustrated by the following formula:



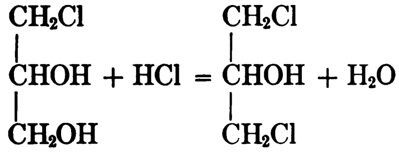
With basic lead acetate and ammonia glycerol forms an insoluble lead glycerate.

When heated with hydrochloric acid, glycerol reacts with the formation of water and the replacement of one or two hydroxyl groups by chlorine:



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + HCl = \begin{array}{l} CH_2Cl \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + H_2O$$

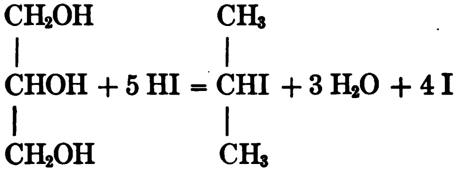
Monochlorhydrin



$$\begin{array}{l} CH_2Cl \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + HCl = \begin{array}{l} CH_2Cl \\ | \\ CHOH \\ | \\ CH_2Cl \end{array} + H_2O$$

Dichlorhydrin

This reaction cannot be effected by the use of hydriodic acid, since the latter acts as a strong reducing agent, owing to the great tendency it shows to separate free iodine, thus making available nascent hydrogen for the abstraction of oxygen. Thus on heating glycerol with five molecular equivalents of hydriodic acid, isopropyl iodide is produced:



$$\begin{array}{lcl} CH_2OH & & CH_3 \\ | & & | \\ CHOH + 5\,HI & = & CHI + 3\,H_2O + 4\,I \\ | & & | \\ CH_2OH & & CH_3 \end{array}$$

Isopropyliodide

Under carefully regulated conditions this reaction is nearly quantitative, and on the measurement of the iodine in the isopropyl iodide produced from a sample depends the quantitative estimation of glycerol proposed by Zeisel and Fanto.

Glycerol is readily oxidized, *i.e.* it exerts a reducing action (abstraction of oxygen) on Fehling's solution even in the cold, owing to its conversion into glyceraldehyde (**36**).

26. Erythritol or Erythrite,

$$CH_2OH—(CHOH)_2—CH_2OH,$$

exists in nature in certain algæ.

27. The Sulphur Alcohols. Mercaptans. — Just as the alcohols are derivatives of water, formed by replacing one of the hydrogen atoms by an alkyl group, so also there exists a class of compounds of analogous constitution derived from hydrogen sulphide. These are known as *thio-alcohols*, *mercaptans*, or alkyl sulph-hydrates:

$H—O—H$	$R—O—H$	$H—S—H$	$R—S—H$
Water	Alcohol	Hydrogen sulphide	Mercaptan

They are formed by warming alkyl halides with potassium sulph-hydrate in concentrated aqueous or alcoholic solution:

$$C_2H_5I + KSH = \underset{\text{Mercaptan}}{C_2H_5SH} + KI$$

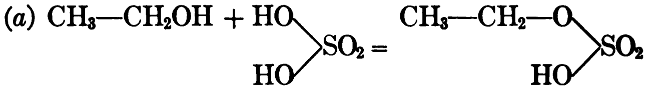
Methyl mercaptan, CH_3SH, is a gas, B. P. 6°. It is produced by the action of anaërobic bacteria on proteins, being one of the products of putrefaction. It has a disgusting odor. It is a constituent of intestinal gases.

Ethyl mercaptan, $CH_3—CH_2SH$, is a liquid with an extremely obnoxious odor; B. P. 36°. It reacts with sodium, forming C_2H_5SNa, analogous to sodium alcoholate.

CHAPTER III

ESTERS AND ETHERS

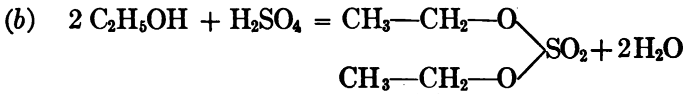
28. Esters. — When alcohols are treated with acids which have a strong affinity for water, a reaction may take place in which a molecule of water and a new compound called an *ester* are produced. Thus the action of hydriodic acid on alcohol with the production of an alkyl halide (**20**) is representative of a general type of reaction. Thus:



$$(a)\ CH_3{-}CH_2OH + \begin{matrix}HO \\ HO\end{matrix}{>}SO_2 = \begin{matrix}CH_3{-}CH_2{-}O \\ HO\end{matrix}{>}SO_2$$

Alcohol Sulphuric acid Ethyl sulphuric acid

Compounds of the type of ethyl sulphuric acid are known as *ethereal acids.*

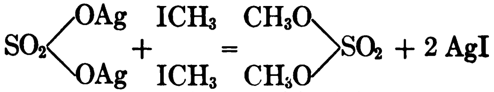


$$(b)\ 2\,C_2H_5OH + H_2SO_4 = \begin{matrix}CH_3{-}CH_2{-}O \\ CH_3{-}CH_2{-}O\end{matrix}{>}SO_2 + 2H_2O$$

Diethyl sulphate

Diethyl sulphate is a neutral ester.

These compounds can also be formed by the action of the silver salts of the acids on the alkyl iodides:

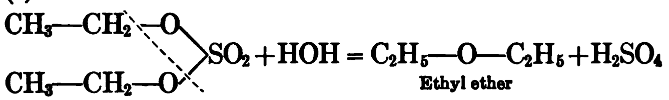


$$SO_2{<}\begin{matrix}OAg \\ OAg\end{matrix} + \begin{matrix}ICH_3 \\ ICH_3\end{matrix} = \begin{matrix}CH_3O \\ CH_3O\end{matrix}{>}SO_2 + 2\,AgI$$

Silver sulphate Methyl iodide Dimethyl sulphate

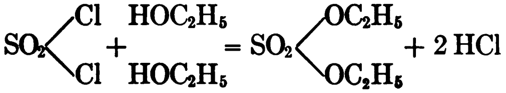
Diethyl sulphate is a colorless oily liquid possessing a peppermint odor. It is insoluble in water: It boils at 208°. It is readily hydrolysed, *i.e.* broken up with the entrance of water into the compound, but the original substances, alcohol and sulphuric acid, from which it was formed, are not regenerated. Instead diethyl ether is produced (**29**).

(*c*)



$$\begin{matrix} CH_3-CH_2-O \\ CH_3-CH_2-O \end{matrix}\!\!>SO_2 + HOH = \underset{\text{Ethyl ether}}{C_2H_5-O-C_2H_5} + H_2SO_4$$

The structure of diethyl sulphate is also shown by its formation from alcohol and sulphuryl chloride, SO_2Cl_2.



$$SO_2\!\begin{matrix} \diagup Cl \\ \diagdown Cl \end{matrix} + \begin{matrix} HOC_2H_5 \\ HOC_2H_5 \end{matrix} = SO_2\!\begin{matrix} \diagup OC_2H_5 \\ \diagdown OC_2H_5 \end{matrix} + 2\,HCl$$

(*d*) **Ethyl Sulphuric Acid** is a strongly acid liquid of an oily character and possesses no odor. It is soluble in water in all proportions. It is obtained by mixing alcohol with strong sulphuric acid. The calcium and barium salts are soluble while barium sulphate is insoluble. The solution containing ethyl sulphuric acid, alcohol, and sulphuric acid is neutralized with $BaCO_3$ and the $BaSO_4$ filtered off. On adding just enough sulphuric acid to combine with the barium in the filtrate the barium is removed and free ethyl sulphuric acid is left in solution. It is not very stable, decomposing slowly into alcohol and sulphuric acid in the presence of water at ordinary temperatures and quickly on boiling. Potassium ethyl

It is a liquid which boils at 66°. It has a pleasant odor. It is soluble in water

Ethyl nitrate, $CH_3—CH_2O—NO_2$, is produced directly from its components and resembles methyl nitrate. It boils at 86°, has a sweet taste, but a bitter after taste. It is soluble in alcohol and ether.

Both of these substances are explosive when heated quickly.

Amyl nitrate, $C_5H_{11}ONO_2$, is prepared in an analogous manner. It is a colorless liquid which boils at 148°.

(*h*) Two esters of nitrous acid are important because of their pharmacological properties. They are ***ethyl nitrite***, which is frequently called nitrous ether. It is a gas which boils at − 12°.

$$C_2H_5OH + \underset{\text{Nitrous acid}}{HONO} = \underset{\text{Ethyl nitrite}}{C_2H_5ONO}$$

It is employed in solution in ethyl alcohol (15 %).

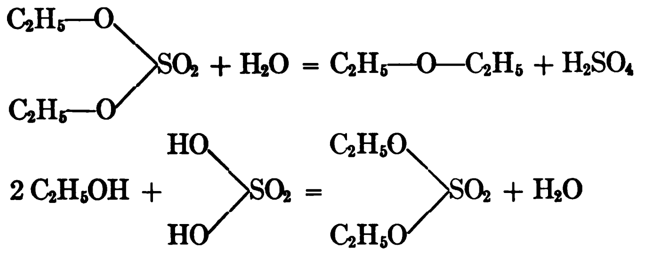
Amyl nitrite boils at 99°. Its physiological action is distinct from that of amyl nitrate.

29. Ethers. — Just as a molecule of alcohol and one of an acid can be condensed with the formation of one of an ester and one of water, so two molecules of alcohol can be condensed with the loss of water to form an ether:

$$(a)\ \text{Alcohol} + \text{Acid} = \text{Ester} + \text{Water}$$

$$(b)\ CH_3\boxed{OH + H}OCH_3 = \underset{\text{Methyl ether}}{CH_3—O—CH_3}$$

The formation of ethyl ether, which is the most common one and is usually referred to as *ether*, has been described in connection with the hydrolysis of the ester diethyl sulphate (**28** *c.*). In practice it is prepared by dropping alcohol continuously into a solution of ethyl sulphuric acid heated to 140–145° C.



$$\left.\begin{matrix}C_2H_5{-}O\\C_2H_5{-}O\end{matrix}\right\rangle SO_2 + H_2O = C_2H_5{-}O{-}C_2H_5 + H_2SO_4$$

$$2\,C_2H_5OH + \left.\begin{matrix}HO\\HO\end{matrix}\right\rangle SO_2 = \left.\begin{matrix}C_2H_5O\\C_2H_5O\end{matrix}\right\rangle SO_2 + H_2O$$

Diethyl sulphate is alternately formed and decomposed and the ether distills over, together with some alcohol and SO_2. From this it would appear that since the sulphuric acid is constantly being regenerated it should act over and over again so that a small amount should induce the formation of ether indefinitely. This is not the case, for the following reason: With the formation of each molecule of ether there is likewise produced a molecule of water. Now ethyl sulphuric acid is readily hydrolyzed to alcohol and sulphuric acid in the presence of water, and in any solution containing these three substances there will be established a state of equilibrium in which there will exist a definite relationship between the amount of alcohol, ethyl sulphuric acid, sulphuric acid, and water. Increasing the concentration of alcohol will cause the formation of more ethyl sulphuric acid, while adding water causes the saponification of some of the ethyl sulphuric acid into its components. The water which is produced in the formation of ether distills over to some extent, but a part remains behind in the still. This tends therefore to cause a progressive decrease in the amount of ethyl sulphuric acid in the flask, so that after a time little or no ether is formed. Instead the alcohol distills over as fast as added. The latter is removed from the distillate by neutralizing the H_2SO_3 with milk of lime. The alcohol passes principally into the water layer, and the ether, which is separated from the water layer in a separatory funnel, is again distilled.

The last traces of water and alcohol are removed from ether by placing in it granulated calcium chloride, which has a strong affinity for both these substances.

Ethyl ether boils at 34.97°. It has an agreeable odor. Prolonged breathing of it causes loss of consciousness. It is much employed in surgery as an anæsthetic. One volume dissolves in 11.1 volumes of water at 25°, and ether dissolves water to the extent of about a 2% solution by volume at 12°. It is much less soluble in a saturated salt solution. With air ether vapors produce highly explosive mixtures. Great care should be exercised therefore in handling ether wherever there is a possibility of ignition, as during distillation. It is best to place the distillation flask in hot water and to dispense with a flame. A small flask should be employed and fresh portions of ether added from time to time, as the distillation proceeds. Small receivers frequently emptied are preferable to one large one.

Ether dissolves a great variety of chemical substances and is indispensable as a solvent in chemical work. In many instances substances can be separated from complex mixtures by extracting a water solution with ether. This depends upon the fact that when a substance is soluble in two liquids which do not mix, as ether and water, it will, when water and ether are shaken together and then allowed to separate into two layers, distribute itself between the ether and the water. If now the ether be separated from the water by means of a separatory funnel, and fresh ether shaken with the water, a division of the dissolved substance will again take place. In this manner by shaking repeatedly with fresh portions of ether the water solution becomes progressively poorer in the dissolved substance. The ether on evaporation leaves behind the material which it contained.

The constitution of the ethers is further shown by their formation from an alcoholate and an alkyl halide:

$$\underset{\text{Sodium ethylate}}{C_2H_5O}\boxed{Na + I}C_2H_5 = C_2H_5\text{—}O\text{—}C_2H_5 + NaI$$

This reaction serves to show what actually happens when sodium reacts with an alcohol (**15**). There are two possibilities. The sodium might replace one of the hydrogen atoms which is linked with carbon, or that one which is linked to oxygen. If the former were true, we should have formed a compound of the following structure:

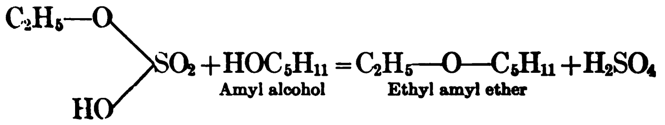
$$CH_3\text{—}OH + Na = NaCH_2OH$$

On causing this to react with an alkyl iodide there should be formed a *higher alcohol:*

$$CH_3I + NaCH_2\text{—}OH = CH_3\text{—}CH_2\text{—}OH + NaI$$

The formation of ethers in this way proves that in these the two alkyl groups are linked together through oxygen. This is called Williamson's reaction, after the name of its discoverer.

If to the mixture of alcohol and sulphuric acid (containing ethyl sulphuric acid) there is added, beginning just before distillation commences, an alcohol other than ethyl alcohol, a *mixed* ether will result. In this way numerous ethers containing different alkyl radicals can be produced.



$$\left.\begin{matrix}C_2H_5-O\\ \\ HO\end{matrix}\right>SO_2+\underset{\text{Amyl alcohol}}{HOC_5H_{11}}=\underset{\text{Ethyl amyl ether}}{C_2H_5-O-C_5H_{11}}+H_2SO_4$$

This furnishes further evidence that the steps in the formation of ether are as described above.

CHAPTER IV

THE ALDEHYDES AND KETONES

30. Oxidation Products of the Alcohols. — It has long been known that alcohol-containing solutions, as fermented cider, wine, or beer, soon become sour when exposed to the air in open vessels at room temperature. *Vinegar* is formed through the change of alcohol into *acetic acid*. In the absence of oxygen this change does not take place, and it is greatly accelerated by thorough aëration of the solution, as by causing it to pass through porous material. The oxidation is not spontaneous, but results from the growth in the solutions of a microörganism *Mycoderma aceti*, or "mother of vinegar." If the vessel containing the alcoholic solution which is undergoing this change admits but an inadequate supply of air (oxygen) there accumulates an intermediary product known as *aldehyde* or, from its relation to acetic acid, *acetaldehyde*.

The change which takes place in these processes is shown by the following equations:

$$CH_3—CH_2OH + O = \underset{\text{Acetaldehyde}}{CH_3—CHO} + H_2O$$

$$CH_3—CHO + O = \underset{\text{Acetic acid}}{CH_3—COOH}$$

Oxygen of the air (molecular oxygen) cannot effect this oxidation, except through the agency of an "oxygen carrier," or catalyzer, which "activates" it. This action is brought about by the presence in the acetic acid organism of *oxydases*.

Numerous examples are known of the activation of molecular oxygen through the agency of inorganic catalyzers. Thus a mixture of hydrogen and air is stable at ordinary temperatures and can be left for a long period without the hydrogen and oxygen combining to form water. If a platinum spiral be introduced into such a mixture, the volume of the gas mixture will decrease noticeably and the platinum grow warm. The hydrogen and oxygen will now rapidly combine. If instead of a platinum spiral very finely divided metal, platinum sponge, be employed, the two elements may combine with explosive violence.

Another example of the effect of an inorganic catalyzer is seen in the technical process of converting methyl alcohol into formaldehyde. Air and methyl alcohol in the proper proportions to supply oxygen for the oxidation of the alcohol form a relatively stable mixture. It can be heated to a relatively high temperature without any oxidation taking place. If however a copper gauze which has been oxidized on its surface be warmed gently and the air-alcohol mixture passed slowly over it, the oxidation of the alcohol is rapidly effected, water and formaldehyde being formed. The heat generated by the oxidation serves to keep the copper in a glowing condition:

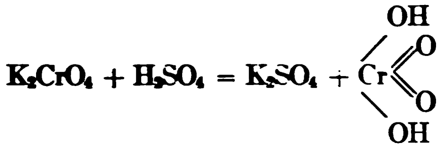
$$CH_3OH + O = \underset{\text{Formaldehyde}}{HCHO} + H_2O$$

The exact nature of the process by which these accelerations of reactions is brought about is not known with certainty. The amount of acceleration depends upon the amount of surface of metal or oxide exposed to the reacting mixture, and it is known that platinum can absorb relatively large amounts of certain gases, and the more the greater the degree of fineness of its division. Since the more finely divided the metal the greater the surface exposed, the reason for the higher efficiency of the metal in a fine state of division becomes apparent. The catalytic action is most simply explained by assuming that the gases dissolve in the surface layer of the metal and therefore exist in much more concentrated state by which more molecules are brought together for interaction in a given time.

For the preparation of acetaldehyde, which is for brevity ordinarily referred to as aldehyde, in the laboratory the oxidation of alcohol is effected by chromic acid:

$$3\,C_2H_5OH + 2\,K_2CrO_4 + 5\,H_2SO_4$$
$$= 3\,\underset{\text{Aldehyde}}{CH_3{-}CHO} + Cr_2(SO_4)_3 + 2\,K_2SO_4 + 8\,H_2O.$$

In this reaction the sulphuric acid first reacts with the potassium chromate, forming chromic acid:



$$K_2CrO_4 + H_2SO_4 = K_2SO_4 + Cr(OH)_2O_2$$

The chromium in the chromic acid gives up its oxygen to the alcohol, passing from the hexavalent to the trivalent state.

The green color of the chromous sulphate and the fruity odor of the aldehyde are so characteristic that this reaction

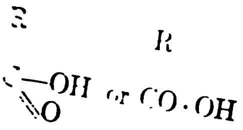
[illegible]

[illegible] to the [illegible] The [illegible] in this way [illegible] [illegible] and the formation [illegible]

[illegible]—OH — HCl
[illegible] — HCl

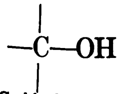
[illegible]ehydes and Acids. — The [illegible] and their [illegible] acid [illegible] primary [illegible] cor- [illegible] the aldehydes [illegible] less [illegible] hydrogen [illegible] the acids [illegible] the aldehydes cor- [illegible]

[illegible] assigned to these three [illegible]



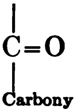
Acid

The primary alcohols, the aldehydes and corresponding acids are derived from the hydrocarbons by the substitution of a hydrogen atom linked to a primary carbon atom by the following groups:



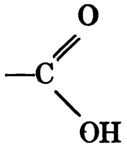
$$-\overset{|}{\underset{|}{C}}-OH$$

Carbinol group
(Alcohol)



$$\overset{|}{\underset{|}{C}}=O$$

Carbonyl
group
(Aldehyde
or Ketone)



Carboxyl group
(Acid)

The behavior of these groups when acted upon by PCl_5 throws further light upon their structure. Thus the alcohols yield, as already pointed out, alkyl halides, the OH acting as a unit and being replaced by Cl, a monovalent element. When PCl_5 acts upon aldehydes, the oxygen is replaced by two Cl atoms forming dichlor hydrocarbons. With the organic acids PCl_5 replaces the OH group as in the alcohols and leads to the formation of *acid chlorides:*

$$CH_3-CH_2OH + PCl_5 = \underset{\text{Ethyl chloride}}{CH_3-CH_2Cl} + POCl_3 + HCl$$

$$CH_3-CHO + PCl_5 = \underset{\text{Ethylidene chloride}}{CH_3-CHCl_2} + POCl_3$$

$$CH_3-COOH + PCl_5 = \underset{\text{Acetyl chloride}}{CH_3-COCl} + POCl_3 + HCl$$

32. Properties of the Aldehydes. — (1) The aldehydes are characterized by exceptional chemical activity. They are easily oxidized, slowly by contact with the air and quickly by oxidizing agents such as chromic acid. They possess therefore marked *reducing properties,* and abstract oxygen from the oxides of the noble metals. They reduce an ammoniacal solution of silver oxide or silver salts, caus-

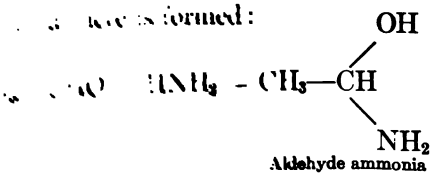
[illegible] metallic silver. Some of the aldehydes [illegible] alkaline copper solutions, especially [illegible] sodium hydroxide. This property is [illegible] and delicate to be of use as a [illegible] estimating aldehydes (Fehling's [illegible]

[illegible] aldehydes are easily reduced by nascent [illegible] same primary alcohols from which they [illegible] oxidation

$$[illegible]\,CHO + 2H = CH_3CH_2OH$$

[illegible] dichlor derivatives of the type [illegible] halogen) (**31**).

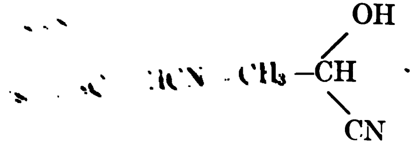
[illegible] reactions: (a) Aldehydes react with [illegible] hydrocyanic acid to form addition products. [illegible] is formed:



$$[illegible]\;NH_3 = CH_3{-}CH\begin{matrix}OH\\NH_2\end{matrix}$$

Aldehyde ammonia

[illegible] of aldehyde and HCN is of [illegible] it forms a method of building [illegible] which are at the same time [illegible]

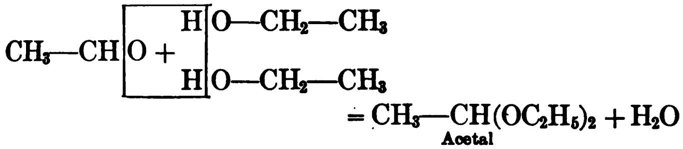


$$[illegible]\;HCN = CH_3{-}CH\begin{matrix}OH\\CN\end{matrix}$$

Ethylidene cyanhydrin

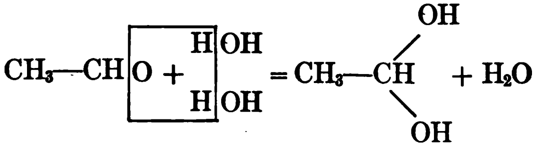
[illegible] is readily transformed into

(*b*) Upon heating with alcohols, stable ethers — the "acetals" — are formed:



$$CH_3-CH\boxed{O+\begin{matrix}H\\ \\H\end{matrix}}\begin{matrix}O-CH_2-CH_3\\ \\O-CH_2-CH_3\end{matrix} = CH_3-\underset{\text{Acetal}}{CH(OC_2H_5)_2} + H_2O$$

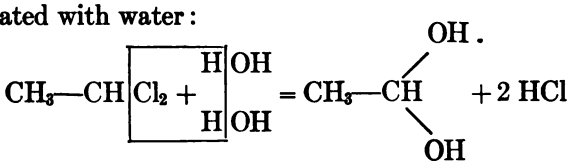
This reaction would lead to the supposition that the aldehydes could react with water to form dialcohols having both of the OH groups linked to one carbon atom:



$$CH_3-CH\boxed{O+\begin{matrix}H\\ \\H\end{matrix}}\begin{matrix}OH\\ \\OH\end{matrix} = CH_3-CH\begin{matrix}\diagup OH\\ \\ \diagdown OH\end{matrix} + H_2O$$

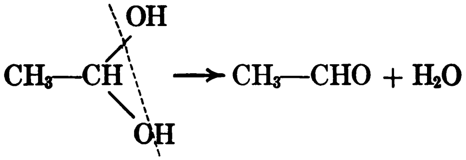
Ethylidene glycol
(Hypothetical)

This same compound, the hypothetical *ethylidene glycol*, we should expect to be formed when ethylidene chloride is heated with water:



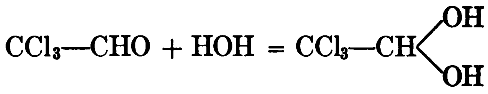
$$CH_3-CH\boxed{Cl_2+\begin{matrix}H\\ \\H\end{matrix}}\begin{matrix}OH\\ \\OH\end{matrix} = CH_3-CH\begin{matrix}\diagup OH.\\ \\ \diagdown OH\end{matrix} + 2\,HCl$$

This does not appear to be the case. If it is formed its existence is but momentary, the compound being immediately broken down into the aldehyde and water:



$$CH_3-CH\begin{matrix}\diagup OH\\ \\ \diagdown OH\end{matrix} \longrightarrow CH_3-CHO + H_2O$$

From such considerations the conclusion may be drawn that two hydroxyl groups cannot as a rule exist bound to the same carbon atom. A molecule of water is separated and an oxygen atom becomes bound to the carbon atom by both its affinities instead. When several negative atoms in the radical are introduced in place of hydrogen such hydrates can exist. Thus trichlor acetaldehyde, commonly called *chloral*, combines with water to form chloral hydrate:



$$CCl_3—CHO + HOH = CCl_3—CH\begin{matrix} \diagup OH \\ \diagdown OH \end{matrix}$$

Chloral Chloral hydrate

This compound does not behave like a diatomic alcohol, however, but like the aldehyde from which it was derived, owing to the ease with which water is separated.

(5) The aldehydes polymerize readily. By polymerization is meant the transformation of a compound into another having the same percentage composition with respect to the elements, but with a molecular weight which is a multiple of that represented by the simplest formula. In the case of formic aldehyde this change is spontaneous at the ordinary temperatures. Acetaldehyde does not polymerize so readily, but the change is brought about by the presence of traces of hydrochloric, sulphuric, or sulphurous acid, zinc chloride, etc. The reason for their catalytic effect is unknown.

Alkalies induce a different kind of polymerization of aldehydes, leading to the formation of *aldehyde resins*. For acetaldehyde this is reddish brown in color, insoluble in water, but soluble in alcohol, and gives off a peculiar odor which is characteristic.

Formic aldehyde, on the other hand, in the presence of alkali shows the phenomenon known as the *Cannizarro reaction,* in which through the action of water one molecule of aldehyde is oxidized to acid, and another is reduced to an alcohol, thus:

$$2\,HCHO + H_2O = CH_3OH + \underset{\text{Formic acid}}{HCOOH}$$

(6) The aldehydes show a tendency to form condensation products in which two molecules combine with a rearrangement of the bonds of the carbon atoms, a hydrogen atom of one molecule changing its linkage from carbon to oxygen with the formation of a hydroxyl group. Thus when aldehyde stands in contact with acids or alkalies it undergoes what is known as the *aldol condensation.* There is formed β-oxybutyric aldehyde:

$$CH_3CHO + CH_2H{-}CHO = \underset{\beta\text{-oxybutyric aldehyde (Aldol)}}{CH_3{-}CH(OH){-}CH_2{-}CHO}$$

This property of the aldehydes is of fundamental importance in biology, for the formation of carbohydrates, fats, proteins, etc., which occur in the animal and vegetable kingdoms.

Formic aldehyde does not condense through the influence of acids, but does so readily through the influence of very weak alkalies, even calcium carbonate greatly accelerating the action. The condensation products of formaldehyde will be considered in detail in connection with the synthesis of the sugars (**151**).

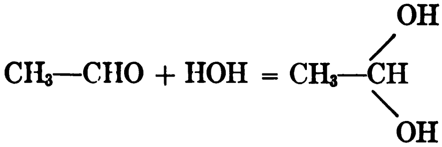
(7) With hydroxylamine, NH_2OH, aldehydes condense to form *aldoximes*, water being formed in the reaction:

$$CH_3CHO + NH_2OH = CH_3—CH{=}N—OH + H_2O$$

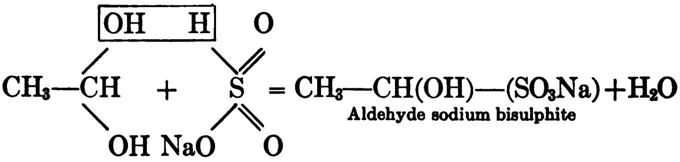
(8) With hydrazine, $NH_2—NH_2$, or its substitution products, aldehydes condense to form *hydrazones*, compounds containing two nitrogen atoms:

$$CH_3CHO + NH_2—NHR = CH_3—CH{=}N—NHR + H_2O$$

(9) The aldehydes react with sodium bisulphite to form crystalline compounds which are readily soluble in water, but sparingly so in alcohol. These are looked upon as sulphonic acid esters of the hypothetical ethylidene glycol:



$$CH_3—CHO + HOH = CH_3—CH\begin{cases}OH\\OH\end{cases}$$

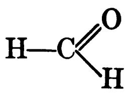


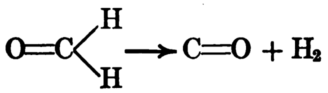
$$CH_3—CH\begin{cases}\boxed{OH \quad H}\\OH\end{cases} + \begin{matrix}H\\NaO\end{matrix}\!>S\!\begin{matrix}\!/\!\!/O\\ \!\backslash\!\!\backslash O\end{matrix} = CH_3—CH(OH)—(SO_3Na) + H_2O$$

Aldehyde sodium bisulphite

Such compounds are easily broken up on warming with a solution of sodium carbonate, with the re-formation of aldehydes. These compounds are of great importance, therefore, in the isolation of aldehydes.

Nomenclature. — The aldehydes are named from the hydrocarbons from which they are derived with the termination *-al*. Several of the more important ones have long had names which do not correspond to this system of nomenclature.

33. Formaldehyde. —  $H{-}C{\overset{O}{\underset{H}{\lessgtr}}}$ (Methanal). Results from the regulated oxidation of methyl alcohol, employing a glowing platinum or copper spiral as a catalyzer (**30**). Other oxidizing agents acting on methyl alcohol do not yield the aldehyde. Instead the oxidation goes farther, formic acid being produced (**50**). It is a gas which when cooled strongly condenses to a liquid which boils at – 21°. Formaldehyde is formed by the direct union of hydrogen and carbon monoxide under the influence of the silent electrical discharge. At 600° C. it is again dissociated into hydrogen and carbon monoxide:



$$O{=}C{\overset{H}{\underset{H}{<}}} \longrightarrow C{=}O + H_2$$

This is an example of the change of carbon from the divalent into the tetravalent state and vice versa. This type of change in the nature of carbon will be further treated under the isonitriles (**40**). Formaldehyde is supplied commercially as a 40 % solution known as formalin.

Formaldehyde is a powerful poison by reason of its power to react with the proteins of the tissues, destroying their special properties as components of the living protoplasm. It is employed in disinfection and in the preservation and hardening of anatomic specimens.

With ammonia it forms hexamethylenetetramine, or *urotropin,* a feebly basic crystalline solid, soluble in 1.8

parts of water and 10 parts of alcohol. (Sometimes also called aminoform and cystamin.)

$$6\,CH_2O + 4\,NH_3 = (CH_2)_6N_4 + 6\,H_2O$$

It is employed internally in medicine as an antiseptic. It is absorbed without decomposition and passes through the kidneys in great measure unchanged, but the urine after its administration frequently contains traces of formaldehyde.

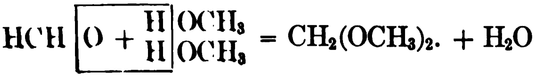
Polymerization of formaldehyde. — According to the conditions formaldehyde polymerizes in different ways.

Paraformaldehyde is formed when formalin is evaporated on a water bath. It is a white solid which melts at about 153° and on strongly heating evolves formaldehyde. It is looked upon as $(CH_2O)_2$.

Trioxymethylene $(CH_2O)_3$ is a white crystalline compound which separates from solutions of formaldehyde on standing. This substance differs from paraldehyde in that it does not dissolve in water, alcohol, or ether. It is formed spontaneously when formaldehyde solution is allowed to evaporate at ordinary temperatures. It passes into formaldehyde again on heating.

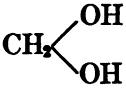
Formose $(CH_2O)_6$ is a condensation product resulting from the action of milk of lime on formaldehyde. It consists of a mixture of sugars of the glucose group (**151**).

Methylal, $CH_2(OCH_3)_2$, may be looked upon as derived from one molecule of formaldehyde and two of methyl alcohol:



$$HCH\,\boxed{O + \begin{matrix}H\\H\end{matrix}}\begin{matrix}OCH_3\\OCH_3\end{matrix} = CH_2(OCH_3)_2. + H_2O$$

It is therefore an ether of the hypothetical glycol



$$CH_2\langle{}^{OH}_{OH}$$

It is employed as a soporific and anesthetic, B. P. 42°. It is soluble in water, in alcohol, and in oils.

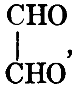
Acetaldehyde (*acetic aldehyde, ethanal, aldehyde*), CH_3CHO. The preparation of this aldehyde by the oxidation of alcohol has already been described (**30**). It is purified by conversion into aldehyde ammonia, which is filtered and washed with ether. The aldehyde ammonia is afterward distilled with dilute sulphuric acid.

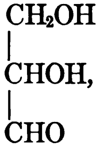
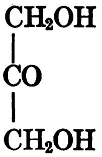
It is obtained in large quantities as a by-product in the distillation of fermented solutions in the manufacture of spirits. It is a colorless liquid, B. P. 21°, specific gravity about .8. It has a characteristic suffocating odor. It is a solvent for sulphur, phosphorus and iodine. Aldehyde dissolves readily in water, alcohol, and ether. PCl_5 converts it into ethylidene chloride (**31**).

Paraldehyde $(C_2H_4O)_3$ is formed when a little HCl, $COCl_2$, SO_2, or $ZnCl_2$ is added to aldehyde. It is formed with a violent reaction on adding concentrated sulphuric acid to aldehyde.

It is a colorless liquid which crystallizes below 10.5°, B. P. 124°. It possesses a peculiar, aromatic, suffocating odor and a warm taste; is soluble in alcohol, ether, oils and chloroform, and in ten parts of water. Specific gravity, .995 at 15°.

Paraldehyde is a hypnotic and antispasmodic, and is used in medicine to a considerable extent.

Glyoxal,  $\begin{matrix}CHO\\|\\CHO\end{matrix}$, results from the oxidation of glycol or may be prepared by oxidizing acetaldehyde with nitric acid at ordinary temperatures. It is not crystallizable, but is a solid when free from water. It forms a bisulphite compound which is useful in its isolation.

36. Glyceraldehyde,  $\begin{matrix}CH_2OH\\|\\CHOH\\|\\CHO\end{matrix}$, results from the oxidation of glycerol by sodium hypobromite or by hydrogen peroxide in the presence of ferrous sulphate. There is always formed with it the isomeric compound,  $\begin{matrix}CH_2OH\\|\\CO\\|\\CH_2OH\end{matrix}$

Dihydroxyacetone

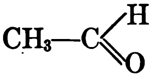
the latter representing the principal product of the oxidation. Glyceraldehyde can also be prepared from acrylic aldehyde (**85**), which confirms its structure.

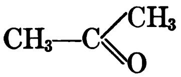
37. Ketones. — When secondary alcohols are oxidized they lose two hydrogen atoms and yield ketones, compounds containing the carbonyl group in a secondary position:

$$(1)\quad \underset{\text{Secondary propyl alcohol}}{CH_3—CHOH—CH_3} + O = \underset{\text{Dimethylketone (Acetone)}}{CH_3—CO—CH_3} + H_2O$$

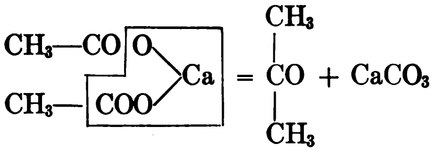
They contain the carbonyl group linked to two carbon atoms, and may be looked upon as aldehydes in which the

H of the CHO group has been replaced by an alkyl group, or as organic acids whose hydroxyl is exchanged for alkyl. The existence of ketones having less than three carbon atoms is theoretically not possible.


Aldehyde

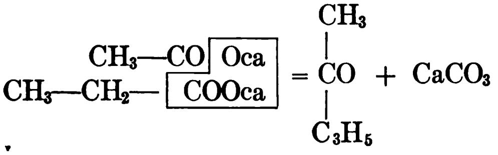

Ketone

(2) Acetone, $CH_3—CO—CH_3$, is also formed by the dry distillation of the calcium or barium salt of acetic acid:

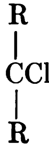


$$\begin{array}{l} CH_3—CO\,O \\ \qquad\qquad\quad >Ca \\ CH_3—COO \end{array} = \begin{array}{c} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{array} + CaCO_3$$

(3) By employing acids having longer carbon chains ketones with higher alkyl groups are formed. Thus a mixture of equal molecules of calcium acetate and calcium propionate, $CH_3—CH_2—COOca$ ($ca = \frac{1}{2}\,Ca$), yields a mixed ketone:



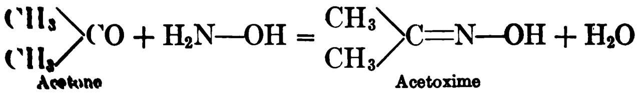
$$\begin{array}{r} CH_3—CO\;Oca \\ CH_3—CH_2—\;COOca \end{array} = \begin{array}{c} CH_3 \\ | \\ CO \\ | \\ C_3H_5 \end{array} + CaCO_3$$

(4) Alkyl dichlorides of the type  $\begin{array}{c} R \\ | \\ CCl_2 \\ | \\ R \end{array}$ react with water to form ketones:

the aldehydes. With hydrocyanic acid, however, there are formed addition products called nitriles. These compounds are of the greatest importance in synthetic chemistry. They will be dealt with in detail later (**40**, **156**).

(4) The ketones differ from the aldehydes in that they do not polymerize. They do form condensation products, however, analogous to the behavior of aldehydes. Acetone, when acted upon by HCl, H_2SO_4, KOH, CaO, and other reagents, condenses with the separation of water. Two molecules unite to form mesityl oxide, $C_6H_{10}O$; three molecules condense to form mesitylene (**172**).

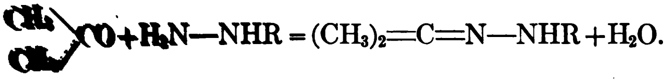
(5) Like the aldehydes, the ketones condense with hydroxylamine to form ketoximes (**31**).



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CO + H_2N—OH = \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>C{=}N—OH + H_2O$$

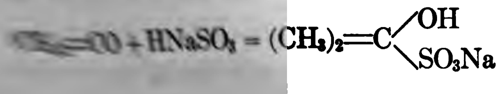
Acetoxime on heating with concentrated HCl decomposes into acetone and hydroxylamine.

In a similar manner, ketones react with the amino group of the hydrazines, forming hydrazones:



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CO + H_2N—NHR = (CH_3)_2{=}C{=}N—NHR + H_2O.$$

Those ketones which contain the radical $CH_3—CO—$, and a few others, form addition products with sodium bisulphite in a manner similar to the aldehydes:



$$(CH_3)_2{=}CO + HNaSO_3 = (CH_3)_2{=}C\begin{matrix}/OH\\ \backslash SO_3Na\end{matrix}$$

These when heated with sodium carbonate solution regenerate ketones. These compounds are of great value in separating ketones from mixtures and in purifying them.

38. Acetone, $CH_3—CO—CH_3$, is the simplest and most common ketone. It is a liquid with a characteristic ethereal odor, B. P. 56°.

Its specific gravity at 0° is 0.81. It is soluble in water, but much less so in solutions of inorganic salts. This property is made use of in separating it from water solutions. It likewise dissolves in all proportions in alcohol and in ether.

It is a very stable substance toward oxidizing agents, not being attacked by cold $KMnO_4$ solutions, but it is oxidized to acetic and formic acids by chromic acid. It is very inflammable and should be handled with caution against the ignition of its vapors. Acetone occurs in normal urine in very small amounts, but is present in large quantities in the urine of diabetic patients. Its formation in the body will be explained later (see acetoacetic acid, **127**).

Lieben's iodoform test for acetone depends upon the fact that alkaline iodine solutions oxidize acetone and form triiodo methane or iodoform. A solution of iodine and KI is added to the solution to be tested and then dilute sodium hydroxide added drop by drop. The iodine color is discharged at once and there separates at once a crystalline deposit of iodoform. The reactions involved are:

$$CH_3—CO—CH_3 + \underset{\text{Potassium hypo-iodite}}{3\ KIO} = \underset{\text{Triodoacetone}}{CH_3—CO—CI_3} + 3\ KOH$$

$$CH_3—CO—CI_3 + KOH = \underset{\text{Potassium acetate}}{CH_3—COOK} + \underset{\text{Iodoform}}{CHI_3}$$

The iodoform can be extracted with ether, and on evaporation of the latter is left as yellow hexagonal plates having a characteristic odor. On the formation of iodoform under these conditions depends the qualitative detection of acetone devised by Vournasos. This test is not characteristic for acetone but is given by alcohol and aldehyde as well.

Acetone in the presence of alkali dissolves mercuric oxide, and this property is made use of in testing for its presence in solution. A mercuric salt, as the chloride or nitrate, is added to the solution to be tested, and then sodium hydroxide to strong alkalinity, and then an equal volume of alcohol. The solution is then filtered and the filtrate acidified with HCl and a layer of $(NH_4)_2S$ solution poured carefully upon it. If mercury is precipitated as the black sulphide, it indicates a positive test. Aldehydes also give this reaction.

Acetone forms with mercuric oxide the compound $2\ CH_3—CO—CH_3 \cdot 3\ HgO$, insoluble in dilute acetic acid; also a white crystalline compound,

$$CH_3—CO—CH_3 \cdot (HgSO_4)_2 \cdot 3\ HgO$$

The latter compound is very insoluble in dilute acetic acid, and its formation is the basis of the test for acetone designed by Deniges.

Acetone does not reduce Fehling's solution. With o-nitro benzaldehyde and sodium hydroxide acetone reacts to form indigo (326).

Sulphonal, a substance used as a soporific, is derived from the condensation product of acetone and mercaptan. When these are mixed and treated with hydrochloric acid they condense with the separation of water:

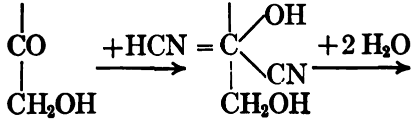
$$\underset{\text{Acetone}}{(CH_3)_2{=}CO} + 2\,\underset{\text{Mercaptan}}{HS{-}C_2H_5} = (CH_3)_2{=}C(SC_2H_5)_2 + H_2O$$

On oxidation this product yields a disulphone, which is *sulphonal.*

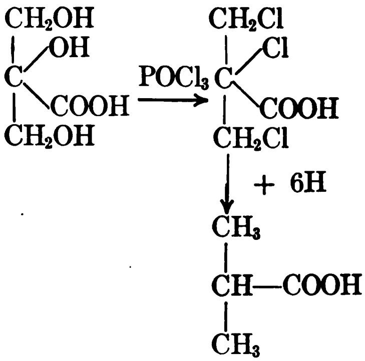
$$(CH_3)_2{=}C(SC_2H_5)_2 + 4\,O = \underset{\text{Sulphonal}}{(CH_3)_2{=}C(SO_2C_2H_5)_2}$$

Several derivatives of higher ketones have also been introduced. Trional is made from ethyl-methyl ketone, and tetronal contains four ethyl groups.

39. Dihydroxyacetone, $CH_2OH{-}CO{-}CH_2OH$, results from the oxidation of glycerol with sodium hypobromite or nitric acid. Its formation is accompanied with that of its isomer glyceraldehyde (36). The structure of dihydroxyacetone is established by the fact that it forms, with hydrocyanic acid, an oxynitrile (32) which by chlorination and subsequent reduction is converted into *isobutyric acid*:



$$\begin{array}{l}CH_2OH\\ |\\ CO\\ |\\ CH_2OH\end{array} \xrightarrow{+HCN} = \begin{array}{l}CH_2OH\\ |\\ C\begin{array}{l}\diagup OH\\ \diagdown CN\end{array}\\ |\\ CH_2OH\end{array} \xrightarrow{+2\,H_2O}$$



Isobutyric acid

Dihydroxyacetone is chemically related to the sugars (150).

CHAPTER V

THE NITRILES AND THEIR REDUCTION PRODUCTS, THE AMINES

40. The Nitriles and Isonitriles. — It has been pointed out (**28**) that alkyl halides react with certain salts of acids, yielding esters, and that these on hydrolysis are resolved into alcohols and acids. The behavior of the salts of hydrocyanic acid is different from others in that it yields two classes of derivatives which do not go back into alcohol and hydrocyanic acid, but yield a new type of compound on hydrolysis:

$$CH_3I + \underset{\text{Potassium cyanide}}{KCN} = \underset{\text{Methyl cyanide}}{CH_3{-}CN} + KI$$

Methyl cyanide is a colorless liquid boiling at 81°. Its specific gravity is .805 at 0°. It is soluble in water and is combustible.

On being warmed with either acids or alkalies nitriles add water (saponification) and are converted into acid and ammonia:

$$CH_3{-}CN + 2\,H_2O = \underset{\text{Acetic acid}}{CH_3{-}COOH} + NH_3$$

This behavior is analogous to that of hydrocyanic acid, which when heated with dilute acids is converted into formic acid and NH_3:

$$HCN + 2\,H_2O = \underset{\text{Formic acid}}{HCOOH} + NH_3$$

Aside from the importance of the nitriles for the formation of acids they are of the greatest importance for building up carbon chains. Thus any alcohol can be converted by PCl_5 into its alkyl halide derivative, and this on being converted into a nitrile gains a new carbon atom:

$$CH_3{-}OH \xrightarrow{PCl_5} CH_3Cl \xrightarrow{KCN} CH_3{-}CN$$
$$\xrightarrow{2\,H_2O} CH_3{-}COOH$$

Two practices prevail regarding the nomenclature of the alkyl cyanides. They are called methyl cyanide, ethyl cyanide, propyl cyanide, etc., but are more frequently called nitriles, and are then named after the acid which they yield on hydrolysis. $CH_3{-}CN$ is called acetonitrile; $CH_3{-}CH_2{-}CN$, propionitrile, etc.

Nascent hydrogen reduces the nitriles to compounds called amines. The process is one of addition of hydrogen:

$$CH_3CN + 4\,H = \underset{\text{Ethyl amine}}{CH_3{-}CH_2{-}NH_2}$$

The amines may be looked upon as ammonia in which one hydrogen atom is replaced by an alkyl group (see amines, 49).

The formation of carboxyl and ammonia on hydrolysis and of amines on reduction shows that in the nitrile the nitrogen cannot be directly linked to the alkyl radical. The CN group is linked to the alkyl group by its carbon.

Isocyanides. If instead of KCN we cause alkyl halide to react with silver cyanide, there is obtained a colorless liquid slightly soluble in water which has an intolerable odor and poisonous properties. It has the same percentage composition with respect to the elements as ethyl nitrile, and is isomeric with it:

$$CH_3{—}CH_2I + AgNC = \underset{\text{Ethyl isocyanide}}{CH_3{—}CH_2{—}NC}$$

This substance behaves on heating with water or with acids in a manner entirely different from ethyl cyanide:

$$CH_3{—}CH_2{—}N \equiv C + 2\,H_2O = \underset{\text{Ethyl amine}}{CH_3{—}CH_2{—}NH_2} + \underset{\text{Formic acid}}{HCOOH}$$

In this compound the carbon atom of the isocyanide is split off, which indicates that the nitrogen is linked directly to the ethyl group. Unlike the nitriles they are very stable toward alkalies.

From the above considerations it appears that the silver salt of hydrocyanic acid has a structure different from that of potassium cyanide.

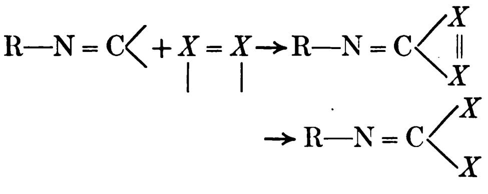
A great interest attaches to the isonitriles or alkyl isocyanides because they apparently form an exception to the general rule that carbon in organic compounds is always tetravalent. Several possible assumptions may be made regarding the structure of these compounds. The carbon atom may be in a divalent state (I); or two of its valences may be free, or polarized (II); or the nitrogen may exist in the pentavalent state (III) as it is known to be, *e.g.*, in ammonium hydroxide, all four valences of the carbon atom being in union with nitrogen.

$$\underset{\text{I}}{R{—}N = C} \qquad \underset{\text{II}}{R{—}N = C\langle \text{ or } R{—}N = C\sqsupset} \qquad \underset{\text{III}}{R{—}N \,≣\, C}$$

The extensive studies of Neff have afforded the most satisfactory explanation of the structure of the isonitriles, and the principles which they disclosed are of great importance in elucidating the nature of reactions generally among organic compounds. A discussion of some reactions which throw light on the behavior of these compounds will be of value.

The isonitriles are assumed by Neff to possess the structure represented by $\mathrm{R{-}N{=}C}$, but there exists a small number of the molecules dissociated into the "active" form $\mathrm{R{-}N{=}C}\langle$, these being in dynamic equilibrium with the form $\mathrm{R{-}N{=}C}$ which, either because its carbon is divalent, or because two of its bonds of affinity are polarized or latent, is incapable of any chemical activity whatever. The percentage of "active" molecules varies with the nature and mass of R, a fact shown by the variation in the chemical activity of compounds of this type.

1. Halogens (chlorine, bromine, iodine), speed of reaction in the order named, are absorbed by the alkyl isocyanides with great evolution of heat, forming dihalogen derivatives:



$$\mathrm{R{-}N{=}C}\Big\langle + \underset{|}{X} = \underset{|}{X} \rightarrow \mathrm{R{-}N{=}C}\Big\langle\begin{matrix}X\\ \|\\ X\end{matrix}$$

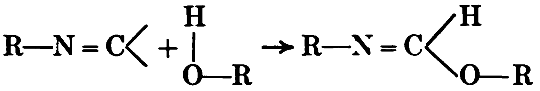
$$\rightarrow \mathrm{R{-}N{=}C}\Big\langle\begin{matrix}X\\ \\ X\end{matrix} \qquad (X = \text{Halogen})$$

2. Oxygen and sulphur convert the isocyanides into isocyanates and isothiocyanates respectively:

$$\mathrm{R{-}N{=}C}\!< + \mathrm{O} \rightarrow \mathrm{R{-}N{=}C{=}O}$$

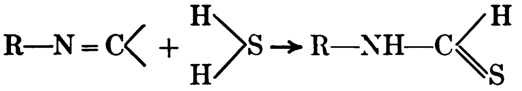
$$\mathrm{R{-}N{=}C}\!< + \mathrm{S} \rightarrow \mathrm{R{-}N{=}C{=}S}$$

3. Alcohols in the presence of alkali are absorbed, giving compounds known as imido ethers:

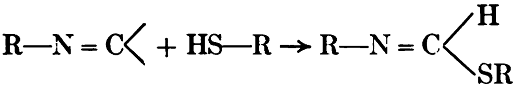


$$\mathrm{R{-}N{=}C}\!< + \begin{array}{l}\mathrm{H}\\ |\\ \mathrm{O{-}R}\end{array} \rightarrow \mathrm{R{-}N{=}C}\!\begin{array}{l}\diagup\mathrm{H}\\ \diagdown\mathrm{O{-}R}\end{array}$$

4. Hydrogen sulphide and mercaptans give the addition products:

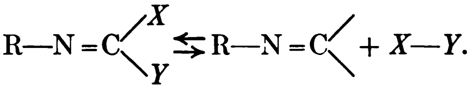


$$\mathrm{R{-}N{=}C}\!< + \begin{array}{l}\mathrm{H}\diagdown\\ \mathrm{H}\diagup\end{array}\!\mathrm{S} \rightarrow \mathrm{R{-}NH{-}C}\!\begin{array}{l}\diagup\mathrm{H}\\ \diagdown\!\!\diagdown\mathrm{S}\end{array}$$



$$\mathrm{R{-}N{=}C}\!< + \mathrm{HS{-}R} \rightarrow \mathrm{R{-}N{=}C}\!\begin{array}{l}\diagup\mathrm{H}\\ \diagdown\mathrm{SR}\end{array}$$

A striking property of these addition products of the isonitriles is their low point of dissociation, *i.e.* the carbon atom which has absorbed the X—Y, thus becoming tetravalent, is unable to hold X—Y above certain temperature limits. There is therefore a certain temperature, varying with the nature of all the groups in the compound, at which the carbon atom becomes spontaneously divalent, the X—Y becoming dissociated, thus:

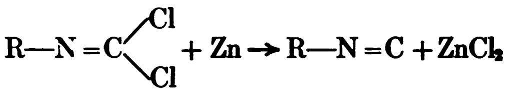


$$\mathrm{R{-}N{=}C}\!\begin{array}{l}\diagup X\\ \diagdown Y\end{array} \rightleftarrows \mathrm{R{-}N{=}C}\!< + X{-}Y.$$

The dissociation is very slight at low and moderate temperatures and increases as the temperature is raised.

There is an equilibrium between divalent and tetravalent carbon.

Dynamic equilibrium implies a set of conditions in which if one of the components of a system is withdrawn, it is replaced by the further dissociation of a part of the undissociated component, so that a definite relationship always exists among the components of the system. Thus the dihalogen addition products of the alkyl isocyanides are converted back into the alkyl isocyanides if kept in contact with zinc dust, the latter serving simply to tie up progressively and remove from the system the small amount of halogen which is dissociated. The dissociation becomes progressive under these conditions and the reaction goes to completion:



$$\mathrm{R{-}N{=}C}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right. + \mathrm{Zn} \rightarrow \mathrm{R{-}N{=}C} + \mathrm{ZnCl_2}$$

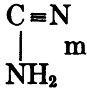
The isonitriles have a marked tendency to polymerize and form resinous products. This is without doubt due to the combination of the active dissociation products with each other, the reaction in this case being non-reversible.

41. Fulminic Acid. — When KCN is oxidized there is produced potassium cyanate, KCNO. There appears to exist an acid isomeric with cyanic acid in fulminic acid. The free acid is not known in a state of purity, but its salts, especially the mercuric and the silver fulminates, are well known. The formulæ for these compounds correspond to $Hg(ONC)_2$ and AgONC.

On hydrolysis the fulminates yield hydroxylamine and a salt of formic acid:

$$\underset{\text{Fulminic acid}}{HONC} + 2H_2O = \underset{\text{Hydroxyl-amine}}{HONH_2} + \underset{\text{Formic acid}}{H—COOH}$$

The formula HONC for fulminic acid can be accepted only by assuming the existence of carbon in a divalent form. This assumption is not ordinarily considered tenable, but there is one compound of carbon, viz. carbon monoxide, which must certainly contain divalent carbon.

42. Cyanamide. —  $\begin{matrix}C\equiv N\\ |\\ NH_2\end{matrix}$ may be regarded as a compound in which a hydrogen of ammonia is replaced by the cyanide radical. The latter is strongly negative and exerts an influence upon the behavior of the hydrogen atoms of the NH_2 group. While ammonia is capable of forming metallic derivatives, these are not readily formed. Sodium and potassium must be strongly heated in the presence of ammonia before the *amides* of these metals are formed ($NaNH_2$, KNH_2) and magnesium must be heated to incandescence in order to form the *nitride*. The hydrogen atoms of the NH_2 or *amide group* in cyanamide are much more easily replaced by metals. Silver cyanamide, $AgHN—C\equiv N$, is a yellow amorphous compound, formed by adding soluble silver salts to solutions of cyanamide. Cyanamide is obtained as the calcium compound by passing nitrogen over heated calcium carbide:

$$CaC_2 + N_2 = \underset{\text{Calcium cyanamide}}{CN \cdot N{=}Ca} + C$$

It is now made on a large scale and is used as a fertilizer.

Calcium cyanamide is slowly decomposed by water, forming calcium carbonate and ammonia:

$$N{\equiv}C{-}N{=}Ca + 3\,H_2O = 2\,NH_3 + CaCO_3$$

As an intermediate product cyanic acid is formed:

$$N \equiv C{-}N = Ca + 3\,H_2O = \underset{\text{Cyanic acid}}{CN{-}OH} + NH_3 + Ca(OH)_2$$

Cyanic acid readily reacts with water to form ammonia and carbon dioxide:

$$N{\equiv}C{-}OH + H_2O = NH_3 + CO_2$$

Cyanamide is a crystalline compound readily soluble in water, alcohol, and ether. It melts at 40°.

43. The Amines. — The hydrogen atoms of ammonia may be replaced by alkyl groups, forming a class of compounds called amines, which have a great biological importance. Many of them occur in nature, especially as products of the action of putrefactive bacteria on proteins. The amines containing the lower alcohol radicals closely resemble ammonia in odor and are even more strongly basic than the latter. Like ammonia, they form white clouds of finely divided salts when brought into contact with volatile acids. The union with acids is attended with the evolution of heat. They behave like ammonia in forming double salts with salts of the heavy metals such as platinic or gold chloride.

They differ from ammonia in being combustible. The lower members are readily soluble in water. The solubility in water diminishes with increasing length of the carbon chains. The volatility likewise diminishes with increasing molecular weight, the highest members being solids insoluble in water and without odor. These are, however, still soluble in alcohol and ether and are basic in character, readily combining with acids to form salts. The specific gravity of all the amines is considerably less than that of water.

Classification. — The amines are termed primary, secondary, or tertiary, depending on whether one, two, or three hydrogen atoms of ammonia are replaced by alkyl groups, *e.g.:*

$$\underset{\substack{\text{Methyl amine}\\ \text{(primary)}}}{CH_3{-}NH_2} \qquad \underset{\substack{\text{Dimethyl amine}\\ \text{(secondary)}}}{(CH_3)_2{=}NH} \qquad \underset{\substack{\text{Trimethyl amine}\\ \text{(tertiary)}}}{(CH_3)_3{\equiv}N}$$

The characteristic group of the primary amines is therefore $-NH_2$, of the secondary amines $=NH$, and of the tertiary amines $\equiv N$.

The relation of the amines to the hydrocarbons is shown by their synthesis from the alkyl halides and ammonia:

$$CH_3I + NH_3 = \underset{\text{Methyl ammonium iodide}}{CH_3{-}NH_2 \cdot HI}$$

Methyl ammonium iodide is a salt entirely analogous to ammonium iodide. On the treating this salt with an alkali, methyl amine is liberated:

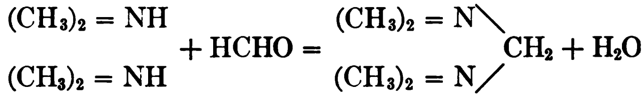
$$CH_3{-}NH_2 \cdot HI + NaOH = CH_3{-}NH_2 + NaI + H_2O.$$

The amines show their character as substituted ammonias in uniting with water to form hydroxides:

$$\underset{\text{Ethylamine}}{CH_3{-}CH_2{-}NH_2} + H_2O = \underset{\text{Ethyl ammonium hydroxide}}{C_2H_5NH_3OH}$$

$$\underset{\text{Dimethylamine}}{(CH_3)_2{=}NH} + H_2O = \underset{\text{Dimethyl ammonium hydroxide}}{(CH_3)_2{=}NH_2OH}$$

$$CH_3—NH_2 + HCHO = \underset{\substack{\text{Methyl-methylene amine}\\ \text{B. P. 166°}}}{CH_3—N = CH_2} + H_2O$$



$$\begin{matrix}(CH_3)_2 = NH \\ (CH_3)_2 = NH\end{matrix} + HCHO = \begin{matrix}(CH_3)_2 = N\diagdown \\ (CH_3)_2 = N\diagup\end{matrix} CH_2 + H_2O$$

Methylene derivative of dimethylamine
B. P. 80–85°

The wide difference in the boiling points of these two compounds makes possible their separation. The bases can be regenerated from the methylene compounds by hydrolysis.

45. *Methods of Preparation.*— (1) The nitro derivatives of the hydrocarbons are reduced by nascent hydrogen, yielding primary amines:

$$CH_3—NO_2 + 6H = CH_3—NH_2 + 2\ H_2O$$

(2) The nitriles, including hydrocyanic acid, can take up four atoms of hydrogen, passing into primary amines:

$$CH_3—CN + 4\ H = CH_3—CH_2NH_2$$

$$HCN + 4\ H = CH_3—NH_2$$

(3) Hydrolysis of alkyl isocyanides yields primary amines and formic acid (**40**).

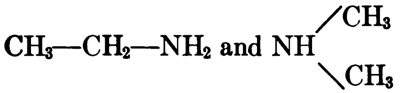
(4) The action of alkyl halides on ammonia has already been referred to (**43**).

(5) The oximes (**32**) are reduced by nascent hydrogen with the formation of primary amines:

$$\underset{\text{Acetaldoxime}}{CH_3—CH = NOH} + 4\ H = CH_3—CH_2—NH_2 + H_2O$$

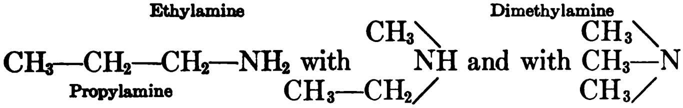
(6) From acid amides by the action of bromine and sodium hydroxide (**53**).

46. *Isomerism of the Amines.*—Two types of isomers of the amines should be mentioned. One is like the isomerism of the ethers, viz. metamerism. Thus:



$$CH_3{-}CH_2{-}NH_2 \text{ and } NH\begin{matrix}\diagup CH_3\\ \diagdown CH_3\end{matrix}$$

Ethylamine Dimethylamine



$$CH_3{-}CH_2{-}CH_2{-}NH_2 \text{ with } \begin{matrix}CH_3\diagdown\\ NH\\ CH_3{-}CH_2\diagup\end{matrix} \text{ and with } \begin{matrix}CH_3\diagdown\\ CH_3{-}N\\ CH_3\diagup\end{matrix}$$

Propylamine Methyl-ethyl amine Trimethylamine

The other depends upon the presence of normal or branched carbon chains as in the alcohols (**9**).

Chemical Behavior.— (1) The amines are not decomposed by saponifying agents, as acids and alkalies, and are oxidized only with great difficulty.

(2) A reaction which distinguishes the primary from the secondary and tertiary amines is their behavior with chloroform. The primary amines react with $CHCl_3$ and alcoholic potassium hydroxide, with the formation of isonitriles. The characteristic odor of the isonitriles (**40**) serves as a delicate qualitative test:

$$CH_3{-}NH_2 + CHCl_3 + 3\,KOH = CH_3{-}N{=}C + 3\,KCl + 3\,H_2O$$

Methyl isocyanide

This is known as Hoffman's carbylamine reaction.

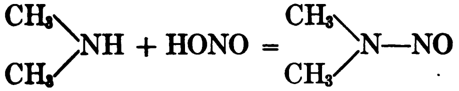
(3) Nitrous acid reacts with primary amines, replacing the $-NH_2$ group by hydroxyl, $-OH$. Elementary nitrogen is liberated from the amino group:

$$CH_3{-}NH_2 + HONO = CH_3OH + N_2 + H_2O$$

This reaction is of great importance in synthetic chemistry, since it makes possible the conversion of amines into the corresponding alcohols.

Recently it has assumed great importance in the eyes of physiological chemists as the result of the discovery by Van Slyke of the conditions necessary for making this reaction the basis of a simple and highly accurate quantitative estimation of amino groups.

With the secondary amines no elementary nitrogen is formed from the imino group =NH. Instead there are formed *nitrosamines*:



$$\begin{matrix} CH_3 \\ CH_3 \end{matrix} \rangle NH + HONO = \begin{matrix} CH_3 \\ CH_3 \end{matrix} \rangle N{-}NO$$

Dimethyl nitrosamine

Dimethyl nitrosamine is an oil with a yellowish color which is readily volatile with steam and can be separated from its mixtures in this way.

Tertiary amines are not acted upon by nitrous acid.

47. **Methylamine**, $CH_3{-}NH_2$, occurs in *Mercurialis perennis* and in the distillate from bones and wood and in herring brine and putrefaction mixtures. It also appears to be a normal constituent of urine, but in very small amounts. It is a gas which greatly resembles ammonia, but its odor is also distinctly fish-like. It is even more strongly basic than ammonia. Its mixtures with air are explosive, and it burns with a yellow flame, in which it differs from ammonia, which is not combustible. One volume of water dissolves at 12.5° 1150 volumes of the gas. It precipitates as double salts the salts of platinum and

gold, and forms methylated ammonium magnesium phosphate, analogous to the ammonium magnesium phosphate.

Methylamine gives with Nessler's reagent (a solution of HgI_2 and KI in potassium hydroxide) a precipitate which is insoluble in an excess of the reagent, or of water. This characteristic serves to distinguish it from the secondary and tertiary amines.

Dimethylamine occurs among the distillation products of wood (pyroligneous acid, **51**) and in guano. It boils at 7°.

Trimethylamine, $(CH_3)_3N$, is found in certain plants, as *Chenopodium vulvaria* and *Arnica montana*, in ergot, and elsewhere. It is a decomposition product of betaine (**63**) and similar plant bases and also of choline (**48**), and results from the action of putrefactive bacteria on materials containing these substances, or through destructive distillation of the same, as in the distillation of vinasse. Some investigators have reported finding traces of trimethylamine in urine, but in the light of recent studies with improved methods it appears that fresh normal urine of man or animals does not contain this base. It has an odor resembling ammonia, but also fish-like. It boils at 3.2°. Its preparation has been described (**43**).

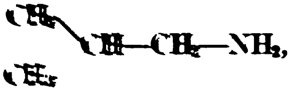
Trimethylamine breaks up when strongly heated, forming methane and hydrocyanic acid:

$$(CH_3)_3{\equiv}N = 2\,CH_4 + HCN$$

Ethylamine, $C_2H_5{-}NH_2$, is formed from alanine (**69**) by destructive distillation, and possibly also by the action of anaërobic bacteria on the same, but its origin through the latter agency has not been demonstrated. It has little biological importance.

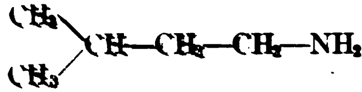
Oxyethylamine, $CH_2OH—CH_2—NH_2$, has been found among the products of hydrolysis of lecithin (96).

Aside from those mentioned the most important aliphatic amines are the following:

Isobutylamine, 

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix} > CH—CH_2—NH_2$$

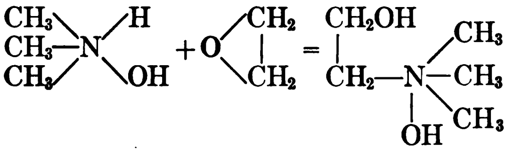
is a liquid which boils at [illegible]. It mixes with water in all proportions. It is formed by putrefactive bacteria acting on amino isovaleric acid, one of the digestion products of the proteins. Its formation will be described later (73). It differs from the primary amines having lower alkyl groups in that it causes a rise of blood pressure in animals.

Isoamylamine, 

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix} > CH—CH_2—CH_2—NH_2$$

boils at [illegible]. It results from the putrefaction of proteins, being derived from the amino acid leucine (75); also on sterile self-digestion (autolysis) of the mushroom, *Boletus edulis*, doubtless formed from leucine. When intravenously injected it raises the blood pressure. With hydrochloric acid it forms a salt, isoamylamine hydrochloride, which is employed to some extent as an antipyretic. Both the free base and its hydrochloride are soluble in water.

Choline is a base of great physiological interest, since it occurs in all cells of both animals and plants and is especially abundant in nervous tissue. It does not occur free in appreciable amount under normal conditions in the animal body, but may accumulate in the cerebrospinal fluid under certain pathological conditions, in which degeneration of nervous tissue is taking place. Choline is always a constituent of certain compounds related to the fats, called *lecithins* (**96**), which are present in large amounts in brain tissue and in egg yolk. From its mode of synthesis it is shown to be a derivative of glycol (**22**), and trimethylamine. It is formed by the condensation of trimethyl ammonium hydroxide with ethylene oxide (**23**).



Choline

The group $—CH_2—CH_2OH$ may be called *oxyethyl.* The name of choline, considering it as a substituted ammonium hydroxide, is trimethyl-oxyethyl-ammonium hydroxide.

Choline is a strong base. In the free state it absorbs moisture and CO_2 readily from the air. Its solutions may be concentrated by boiling to 4 %, when it decomposes into trimethylamine and glycol. Choline is precipitated by a number of reagents, the most efficient being potassium periodide, which precipitates 1 part in 2,000,000 of water.

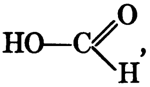
Choline possesses no marked physiological action, but by the action of bacteria and of chemical reagents which abstract water, a base *neurine* is formed, which is 10–20 times more toxic than is choline itself (**97**).

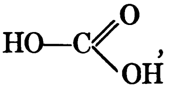
$$\underset{\text{Alcohol}}{\mathrm{R{-}CH_2OH}} \xrightarrow{+\mathrm{O}} \underset{\text{Aldehyde}}{\mathrm{R{-}CHO}} \xrightarrow{+\mathrm{O}} \underset{\text{Acid}}{\mathrm{R{-}COOH}}$$

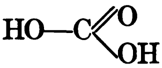
The acids derived from the aliphatic hydrocarbons are called fatty acids because most of them are found as esters in the fats of animals and plants. The lower members of the series are liquids of pungent odor and corrosive action. They boil without decomposition and are readily soluble in water and behave like strong acids.

Formic acid, $HCOOH$, is the lowest member of the series. It occurs free in ants and in the stings of some insects, as bees and caterpillars, and also in certain nettles, in the fruit of the soap tree (*Sapindus saponaria*), and in tamarinds and fir cones. It is always found in traces in perspiration and in urine. It is a colorless liquid with a pungent odor. At 20° its specific gravity is 1.221. It solidifies in a freezing mixture, melts at + 8.3° and boils at 100.8°. Formic acid is readily soluble in water and in many organic solvents. Its vapors are combustible.

It is the strongest acid of the series, being dissociated into H^+ ions to about twelve times the extent of acetic acid. It produces intense irritation of the skin and forms blisters.

Formic acid does not behave like its homologues in certain respects. It is easily oxidized, with the formation of carbon dioxide and water, and therefore possesses strong reducing power, depositing mercury and silver from solutions of their oxides. In this respect it has the properties of an aldehyde, and its ready decomposition through oxidation probably finds its explanation in the acid possessing the formula  $\mathrm{HO{-}C}\langle^{\mathrm{O}}_{\mathrm{H}}$, or hydroxy formaldehyde.

On taking up oxygen the compound, hydroxy formic acid containing two hydroxyls,  $\mathrm{HO{-}C}\langle^{\mathrm{O}}_{\mathrm{OH}}$, is formed. Two hydroxyls cannot remain attached to a single carbon atom, however, except in a few circumstances (see chloral), and water is immediately separated with the liberation of carbon dioxide:



$$\mathrm{HO{-}C}\langle^{\mathrm{O}}_{\mathrm{OH}} = CO_2 + H_2O$$

Formation. — (1) Formic acid is obtained by the oxidation of methyl alcohol:

$$CH_3{-}OH + 2\,O = HCOOH + H_2O$$

(2) Hydrocyanic acid, HCN, behaves as a nitrile in that it can take up two molecules of water, forming the ammonium salt of formic acid:

$$HCN + 2\,H_2O = HCOONH_4$$

From the ammonium salt free formic acid can be obtained by treatment with a nonvolatile acid and distilling:

$$2\,HCOONH_4 + H_2SO_4 = 2\,HCOOH + (NH_4)_2SO_4$$

(3) Carbon monoxide gas, CO, reacts with the caustic alkalies:

$$CO + KOH = \underset{\text{Potassium formate}}{HCOOK}$$

into alcohol and the subsequent oxidation of the alcohol through aldehyde to acid:

$$CH_3—CH_2OH \xrightarrow{+O} CH_3—CHO \xrightarrow{+O} CH_3COOH$$

Its formation is the cause of the souring of beer, wine, and cider. Cider vinegar contains small amounts of alcohol and of acids other than acetic (tartaric, succinic, etc.) and also ethyl esters of these acids, and to these it owes its flavor. It contains usually but 3 to 5 % of acid. The acid volatilizes readily, and in order to obtain it in a pure form from its dilute solutions it is converted into a salt which, being non-volatile, can be heated to evaporate the water. The salt is finally treated with hydrochloric acid, avoiding an excess, and the mixture distilled, when strong acetic acid passes over:

$$(CH_3—COO)_2Ca + 2\,HCl = 2\,CH_3—COOH + CaCl_2$$

Pyroligneous Acid. — When hardwoods are heated in a distilling apparatus, a tarry product containing carbolic acid and related substances is formed, and there distills over a gaseous mixture containing hydrogen, methane, carbon monoxide, and carbon dioxide, a moderate amount of higher hydrocarbons (7 %), and a mixture of water, methyl alcohol, acetone, and acetic acid, together with numerous other compounds in small quantities as impurities. This mixture is known as *pyroligneous acid.* Methyl alcohol and acetone are so readily volatile that they can be distilled from the dilute acetic acid, thus effect-ing a partial separation. The acetic acid is then neutralized with lime, forming calcium acetate, $Ca(OOC—CH_3)_2$, and the latter is then heated to 200° in contact with air to oxidize the tarry matters. From this crude calcium acetate the acetic acid is obtained.

In marked contrast to formic acid, acetic acid is extraordinarily resistant to oxidation. It is not oxidized by chromic acid under any ordinary conditions and can be passed through a glowing tube without decomposition. It is not oxidized by dilute solutions of potassium permanganate, which quickly decompose formic acid. Silver acetate in water solution can be heated without reduction (blackening) taking place.

It is this great stability which explains why acetic acid occurs in such large quantities in the pyroligneous acid. During the decomposition of the various complex compounds (cellulose, lignin, pentosans, etc.) numerous decomposition products are formed which, being unstable at high temperatures, are further decomposed, and in the end only the most stable products remain. Numerous compounds on oxidation yield acetic acid, and owing to its great stability the reaction stops at this point.

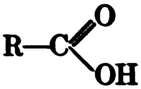
Even the animal body possesses but a very limited capacity to oxidize acetic acid. Normal human urine contains from 60 to 280 mgm. of acetic acid per day.

Acetic acid, despite its stability, is readily fermented in the form of its calcium salt by certain organisms into methane and carbon dioxide:

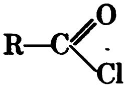
$$CH_3—COOH = CH_4 + CO_2$$

with a known volume of standardized alcoholic potassium hydroxide and heated until the ester is completely hydrolysed, *i.e.* reconverted into acetic acid and alcohol. From the amount of alkali used up in neutralizing the acetic acid which was formed in the hydrolysis the number of hydroxyl groups can be estimated.

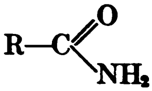
53. The Acid Amides. — The amides may be regarded as organic acids in which the hydroxyl of the carboxyl group is replaced by the amino group, —NH_2:



Acid



Acid chloride



Acid amide

The amides are formed in several ways which illustrate their relationship to other classes of compounds:

(1) Acid chlorides react with ammonia, forming hydrochloric acid and amide:

$$CH_3—COCl + 2\,NH_3 = \underset{\text{Acetamide}}{CH_3—CONH_2} + NH_4Cl.$$

If substituted ammonias (amines) are employed for ammonia, alkylated amides result:

$$CH_3—COCl + 2\,\underset{\text{Methylamine}}{NH_2—CH_3} = \underset{\text{Methyl acetamide}}{CH_3—CO—NHCH_3}$$
$$+ \underset{\text{Methyl-ammonium chloride}}{CH_3—NH_3Cl}$$

(2) The alkyl nitriles react with one molecule of water, forming acid amides:

$$CH_3CN + H_2O = CH_3—CO—NH_2$$

This reaction is the first step in the formation of acid from nitrile. The amides take on a second molecule of water, passing into the ammonium salts of the corresponding acids (50).

Strong dehydrating reagents, such as phosphorus pentoxide, can abstract from the acid amides a molecule of water with the regeneration of nitriles:

$$3\,CH_3—CO—NH_2 + P_2O_5 = 3\,CH_3—CN + 2\,H_3PO_4$$

In order to effect the addition of one molecule of water only, the nitriles are treated with some reagent which contains water, but which has a strong affinity for the latter (*e.g.* strong sulphuric or hydrochloric acid).

(3) By the dry distillation of the ammonium salts of the fatty acids, or by heating them in a closed tube to 230°, water is separated with the formation of the amide:

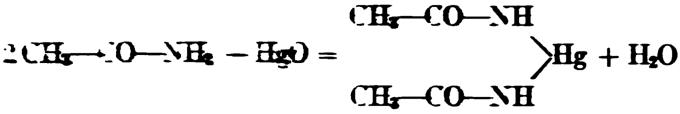
$$CH_3—COONH_4 = CH_3—CO—NH_2 + H_2O$$

(4) Esters can react with ammonia with the production of amides and alcohols:

$$CH_3—COOC_2H_5 + NH_3 = CH_3—CO—NH_2 + C_2H_5OH$$

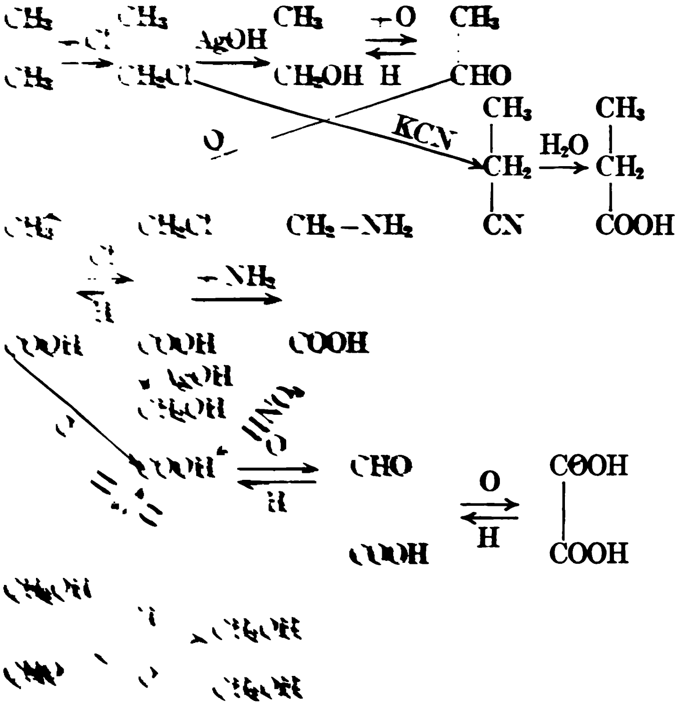
The amides, being derivatives of ammonia, which is strongly basic, formed by the exchange of one hydrogen for an acid radical, possess very feeble basic properties. Thus acetamide forms a salt with hydrochloric acid, which is however very easily decomposed by water. Acetamide hydrochloride is formed when dry hydrochloric acid gas is passed into an ethereal solution of acetamide.

On the other hand the hydrogen of the NH_2 group in the acid amides behaves like acid hydrogen. An aqueous solution of acetamide dissolves mercuric oxide, forming a compound analogous to the salts:



$$2CH_3-CO-NH_2 + HgO = \left.\begin{array}{l} CH_3-CO-NH \\ \\ CH_3-CO-NH \end{array}\right\rangle Hg + H_2O$$

The relationships and mutual transformations among the compounds of the types thus far considered, excluding the ethers and esters, are shown by the following scheme. The series includes some compounds which will be considered immediately:



54. Halogen Derivatives of Acetic Acid. — When chlorine or bromine acts upon acetic acid a substitution of hydrogen by halogen takes place. The resulting products may be mono-, di-, or trichloracetic acid depending on the extent of the substitution.

Chloracetic acid, $CH_2Cl—COOH$, melts at 62.5°. It exerts a corrosive action similar to that of glacial acetic acid on the skin, and the vapors are highly irritating.

Dichloracetic acid, $CHCl_2—COOH$, melts at $-4°$. Its chief interest is its usefulness in syntheses of other compounds.

Trichloracetic acid, $CCl_3—COOH$, is a solid, M. P. 80°. It is extremely caustic in its action on the skin, and is employed for the removal of warts, corns, and similar growths. It is likewise employed as a precipitant for proteins, with which it forms compounds which are relatively insoluble in water or dilute acids.

The acidity of the chlorinated acetic acids, *i.e.* the degree of dissociation of hydrogen ions, increases with increasing chlorine. All are stronger acids than acetic. The strength of trichloracetic acid ranks it with the strong mineral acids.

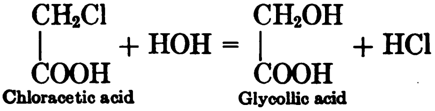
With fatty acids containing three or more carbon atoms chlorine or bromine react to form halogen substituted acids. In all cases the hydrogen substituted is one bound to the carbon atom neighboring the carboxyl group. This is designated the *alpha* carbon atom and is usually abbreviated *α*. Thus:

$$\underset{\text{Propionic acid}}{CH_3—CH_2—COOH} + 2\,Cl = \underset{\alpha\text{-chlorpropionic acid}}{CH_3—CHCl—COOH} + HCl$$

The successive carbon atoms of the fatty acids are designated by the letters of the Greek alphabet, in order of their position, with respect to the carboxyl group. Thus:

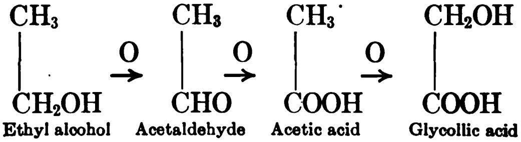
$$\ldots \underset{\delta}{CH_2}—\underset{\gamma}{CH_2}—\underset{\beta}{CH_2}—\underset{\alpha}{CH_2}—COOH$$

55. The Hydroxy Acids. — With water on prolonged boiling the alpha-halogen acids react with the replacement of halogen by hydroxyl. The exchange is greatly facilitated by the presence of silver oxide.

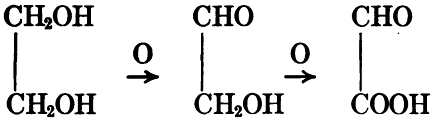


$$\underset{\text{Chloracetic acid}}{\begin{matrix}CH_2Cl\\|\\COOH\end{matrix}} + HOH = \underset{\text{Glycollic acid}}{\begin{matrix}CH_2OH\\|\\COOH\end{matrix}} + HCl$$

Glycollic acid is of interest from the biological standpoint. It may be regarded as an oxyacetic acid. It is found in unripe grapes, in sugar cane, and in many other plants, especially in the green parts. It is taken internally therefore with the food to a slight extent. It is somewhat toxic in large doses. It is a crystalline compound, M. P. 80°, easily soluble in water, alcohol, and ether, but difficultly in acetone. It does not appear in the urine after administration, but has been found after the ingestion of glycol. It is a possible intermediary product of the oxidation of certain complex foodstuffs in the course of metabolism. Its relation to alcohol and glycol, from which it is formed by oxidation, is seen from the following formulæ:



$$\underset{\text{Ethyl alcohol}}{\begin{matrix}CH_3\\|\\CH_2OH\end{matrix}} \xrightarrow{O} \underset{\text{Acetaldehyde}}{\begin{matrix}CH_3\\|\\CHO\end{matrix}} \xrightarrow{O} \underset{\text{Acetic acid}}{\begin{matrix}CH_3\\|\\COOH\end{matrix}} \xrightarrow{O} \underset{\text{Glycollic acid}}{\begin{matrix}CH_2OH\\|\\COOH\end{matrix}}$$

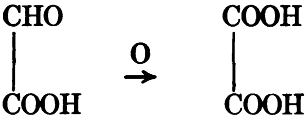


$$\begin{matrix} CH_2OH \\ | \\ CH_2OH \end{matrix} \xrightarrow{O} \begin{matrix} CHO \\ | \\ CH_2OH \end{matrix} \xrightarrow{O} \begin{matrix} CHO \\ | \\ COOH \end{matrix}$$

Glycol Glycol aldehyde Glyoxylic acid

On further oxidation it yields a compound called glyoxylic acid, which is at the same time both an acid and an aldehyde.

Glyoxylic acid is in turn in conformity with its aldehyde nature oxidized to *oxalic acid* (**100**) which contains two carboxyl groups:



$$\begin{matrix} CHO \\ | \\ COOH \end{matrix} \xrightarrow{O} \begin{matrix} COOH \\ | \\ COOH \end{matrix}$$

Oxalic acid

56. The Amino Acids. — Not only can a hydrogen atom of the methyl group of acetic acid be replaced by halogen, hydroxyl, or alkyl group, but also by the amino group —NH_2, with the formation of *amino acids.* In respect to halogen, hydroxyl, and amino derivatives, formic acid behaves very differently from its homologues, acetic, propionic, etc., acids. Thus chlor formic acid $ClCOOH$ is incapable of existence in the free state, but its esters are known. Thus $COCl_2$, which is to be regarded as the acid chloride of chlor formic acid, reacts with alcohols to form chlor formic esters:

$$Cl—CO—Cl + HOC_2H_5 = Cl—COOC_2H_5 + HCl$$

Chlor formic esters

The chlor formic esters behave like acid chlorides, however, in that they are decomposed by water.

Carbamic Acid.— The ammonium salt of amino-formic acid, or *carbamic acid,* is formed when ammonia gas reacts with carbon dioxide:

$$2NH_3 + CO_2 = \underset{\text{Ammonium carbamate}}{NH_2{-}COONH_4}$$

Ammonium carbamate is present as an impurity in commercial ammonium carbonate. On treatment of $NH_2{-}COONH_4$ with a mineral acid it is at once decomposed with evolution of carbon dioxide:

$$NH_2{-}COONH_4 + HCl = NH_4Cl + NH_2{-}COOH$$

$$NH_2{-}COOH = CO_2 + NH_3$$

The metallic salts of carbamic acid are more stable, but decompose at ordinary temperatures in solution into carbonates:

$$NH_2{-}COOK + H_2O = NH_3 + KHCO_3$$

Carbamic acid is distinguished from carbonic acid in the solubility of certain of its salts. Solutions of sodium or potassium carbamate give no precipitate with calcium chloride, as do the corresponding carbonates.

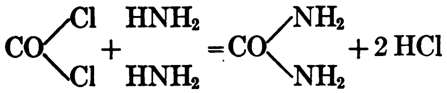
The alkali salts of carbamic acid lose water on heating to redness and pass into the cyanates:

$$NH_2{-}COOK = KCNO + H_2O$$

Ammonium carbamate is an intermediary compound in the formation of urea in the living tissues. Ammonium carbamate on the abstraction of a molecule of water forms the amide of carbamic acid, or *carbamide,* the popular name for the latter being *urea,* a name which was given to the principal nitrogenous compound in the urine of mammals before the development of the science of organic chemistry:

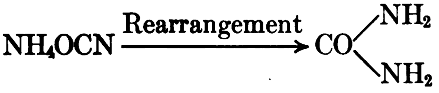
$$NH_2\text{—}COONH_4 = \underset{\text{Urea}}{NH_2\text{—}CO\text{—}NH_2} + H_2O$$

This structure of urea is further confirmed by its formation from carbon oxychloride and ammonia:



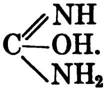
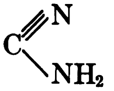
$$CO\begin{matrix}\diagup Cl\\ \diagdown Cl\end{matrix} + \begin{matrix}HNH_2\\ HNH_2\end{matrix} = CO\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix} + 2\,HCl$$

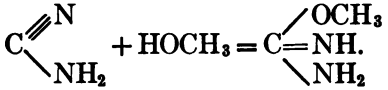
Urea is likewise produced by a rearrangement of the atoms within the molecule of ammonium isocyanate when the latter is heated above its melting point:



$$NH_4OCN \xrightarrow{\text{Rearrangement}} CO\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix}$$

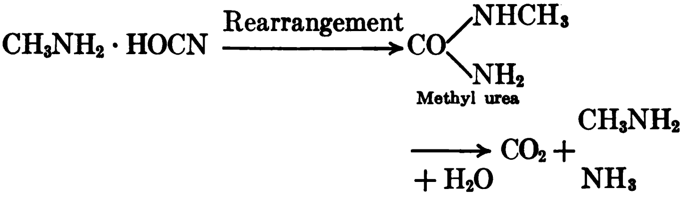
This transformation was observed by Wöhler in 1828 and was the first synthesis of an organic compound. The change of ammonium isocyanate into urea is never quite complete, for a condition is reached where a definite proportion between the isocyanate molecules and urea molecules exists. The reaction is reversible. When silver nitrate is added to a solution of pure urea, silver isocyanate is precipitated. The amount of isocyanate present in such solutions is, however, extremely small, but if removed by the formation of an insoluble compound the reaction proceeds in the direction which leads to its formation. In certain reactions urea behaves as if it had the struc-

ture  $C\begin{array}{l}/\!\!/ NH\\ -OH.\\ \diagdown NH_2\end{array}$ Thus methyl alcohol condenses with cyanamid  $C\begin{array}{l}/\!\!/\!\!/ N\\ \diagdown NH_2\end{array}$ to form *methyl isourea:*



$$C\begin{array}{l}/\!\!/\!\!/ N\\ \diagdown NH_2\end{array} + HOCH_3 = C\begin{array}{l}/ OCH_3\\ = NH.\\ \diagdown NH_2\end{array}$$

The structure is proven by the fact that on heating this compound with hydrochloric acid (hydrolysis) methyl chloride is formed. From *methylurea,* which is formed when the salt of cyanic acid with methylamine (methyl ammonium cyanate) is heated alone, there results, on hydrolysis with hydrochloric acid, methylamine:



$$CH_3NH_2 \cdot HOCN \xrightarrow{\text{Rearrangement}} CO\begin{array}{l}/ NHCH_3\\ \diagdown NH_2\end{array} \xrightarrow[+H_2O]{} CO_2 + \begin{array}{l}CH_3NH_2\\ NH_3\end{array}$$

Methyl urea

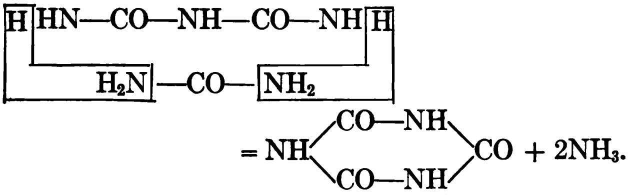
In isomethyl urea the methyl group cannot be linked to nitrogen.

When heated, urea melts and at a higher temperature begins to evolve gas, consisting of ammonia and carbon dioxide. The melt finally solidifies. There are several types of decomposition which take place, the principal ones being the formation of *biuret* and cyanuric acid.

(1) $NH_2—CO—\boxed{NH_2 \quad H}HN—CO—NH_2$

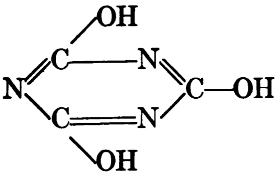
$$= NH_2—CO—NH—CO—NH_2 + NH_3$$

Biuret

(2) 

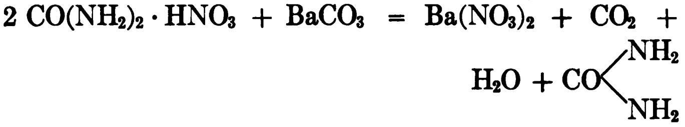
Cyanuric acid

The reactive form of cyanuric acid is probably not that indicated by the above formula. It is a tribasic acid, and forms salts, indicating the presence of three acid hydrogens. It is best represented by the following structural formula:



57. Urea is one of the longest known of organic compounds. It constitutes 85–90 % of the nitrogen of normal human urine. The average amount of urea eliminated daily by a man on an ordinary diet is about 30 grams. The amount may vary greatly with the character of the diet, being high when much protein is eaten and low when the protein intake is low. It is a neutral substance, forming crystals which melt at 130–132°; very soluble in water (1 : 1) and in alcohol (1 : 5 of cold alcohol), but insoluble in ether and chloroform.

Urea is a neutral substance with respect to indicators, but acts as a feeble base in that it forms salts with acids. Urea nitrate, $CO(NH_2)_2 \cdot HNO_3$, is a crystalline compound soluble in water, but slightly soluble in nitric acid. It is slightly soluble in alcohol, but easily in acetone. It is employed for the isolation of urea from urine. The salt is decomposed by barium carbonate:



$$2\,CO(NH_2)_2 \cdot HNO_3 + BaCO_3 = Ba(NO_3)_2 + CO_2 + H_2O + CO\begin{smallmatrix} \diagup NH_2 \\ \diagdown NH_2 \end{smallmatrix}$$

The urea is separated from $Ba(NO_3)_2$ by solution in alcohol. Urea forms salts with other acids, the most important being that with oxalic acid, $[CO(NH_2)_2]_2C_2H_2O_4$. This is a crystalline compound soluble in water, but nearly insoluble in oxalic acid solutions, slightly soluble in alcohol. It is also employed for the isolation of urea from urine.

Urea also forms a compound with mercuric nitrate and mercuric oxide of the formula:

$$2\,CO(NH_2)_2 \cdot Hg(NO_3)_2 \cdot 3\,HgO$$

It likewise forms a compound with mercuric oxide, $CO(NH_2)_2HgO$.

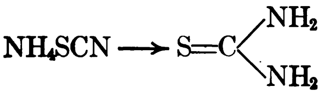
Urea in moderate concentration possesses no appreciable toxicity for the higher animals, but is much more toxic to birds. The latter do not excrete their waste nitrogen as urea, but principally as ammonium urate (**147**). Even in so great dilution as ½ % solutions, urea is noticeably toxic to certain plants. Certain bacteria can employ urea as a source of energy, although it yields very little energy on decomposition. The change which takes place in urea fermentation is as follows:

$$CO(NH_2)_2 + H_2O = CO_2 + 2\,NH_3 + 102 \cdot \text{Calories}$$

Since the fermentation always takes place in solution, the products of the decomposition unite with water to form ammonium carbonate. This decomposition of urea is brought about by an enzyme or organic catalyzer produced by the microörganisms. It has recently been discovered that this enzyme, which is called *urease,* is present in liberal amounts in certain beans, notably the Jack bean and the Soy bean. When an extract of the beans is added to a solution of urea and the mixture protected from bacterial action by toluene, the transformation of urea into ammonium carbonate takes place rapidly and is complete within a few minutes at favorable temperatures. The ammonia is titrated, employing methyl orange as indicator, either directly or after aspirating it into a solution of standard acid. This method was first described by Marshall.

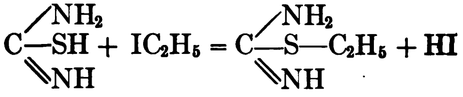
The quantitative estimation of urea by the Folin-Benedict method is effected by converting it into CO_2 and NH_3 by heating the acidified urine in an autoclave. The resulting ammonia is removed by a current of air and is absorbed by a measured quantity of standard acid. A separate determination of ammonia is made on an unheated sample and the result subtracted from that obtained with the heated, the difference representing urea.

58. Thiourea is formed from ammonium isothiocyanate on treating in a manner analogous to the formation of urea from ammonium isocyanate:



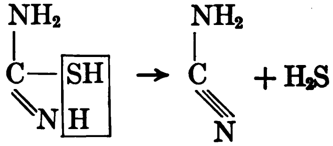
$$NH_4SCN \longrightarrow S{=}C\begin{matrix} \diagup NH_2 \\ \diagdown NH_2 \end{matrix}$$

Thiourea crystallizes readily in very large crystals. It is readily soluble in water but insoluble in alcohol. It melts at 172°. It exhibits the behavior of existing in the tautomeric form in part, for on treatment with alkyl iodide it forms alkyl thioureas which possess the *pseudo* form, the alkyl group being linked to sulphur instead of nitrogen:



Thiourea Pseudo-ethyl-thiourea

That the alkyl group is linked to sulphur is shown by its hydrolysis into ethyl mercaptan instead of ethyl amine, as it would were the ethyl group linked to nitrogen (**57**). When treated with mercuric oxide thiourea loses hydrogen sulphide and forms cyanamide:

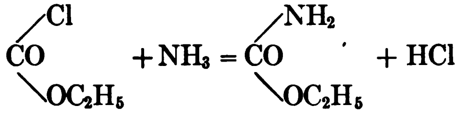


59. Esters of Carbamic Acid. — Carbon oxychloride, $COCl_2$, which is formed by the direct union of carbon monoxide and chlorine in sunlight, can react with alcohol to form the ethyl ester of chlor formic acid:

$$Cl{-}CO{-}Cl + HOC_2H_5 = \underset{\text{Chlor formic ester}}{Cl{-}CO{-}OC_2H_5} + HCl$$

Chlor formic ethyl ester is a volatile liquid of very pungent odor which boils at 93°. It reacts like an acid chloride, being decomposed by water.

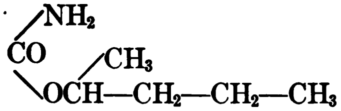
60. Urethanes. — Chlor formic ester reacts with ammonia to form *amino ethyl formate*, the ethyl ester of amino formic acid. This compound is called *urethane:*



$$\mathrm{CO}{<}^{\mathrm{Cl}}_{\mathrm{OC_2H_5}} + \mathrm{NH_3} = \mathrm{CO}{<}^{\mathrm{NH_2}}_{\mathrm{OC_2H_5}} + \mathrm{HCl}$$

Urethane is a colorless crystalline substance possessing a faint peculiar odor and a taste somewhat like that of potassium nitrate. It is soluble in 0.6 parts of alcohol, 1 part of water, 1 part of ether, and in 3 parts of glycerol. It melts at 48–50° and boils at 180°. It is employed as a sedative and hypnotic. A number of derivatives of urethane have been introduced as hypnotics and sedatives in the quest for those which possess the most advantageous properties. Among these may be mentioned:

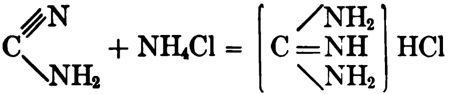
Hedonal is an ester of carbamic acid with the amyl alcohol, methyl propyl carbinol:



$$\mathrm{CO}{<}^{\mathrm{NH_2}}_{\mathrm{O\overset{\displaystyle CH_3}{C}H{-}CH_2{-}CH_2{-}CH_3}}$$

It has a greater hypnotic effect than has urethane. The urethanes are diuretics, as well as hypnotics. In the body they are oxidized to carbon dioxide and urea.

61. Guanidine is formed when cyanamide reacts with ammonium chloride:

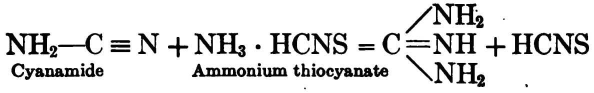


$$\mathrm{C}{<}^{\equiv\mathrm{N}}_{\mathrm{NH_2}} + \mathrm{NH_4Cl} = \left[\mathrm{C}\begin{matrix}\diagup\mathrm{NH_2}\\ =\mathrm{NH}\\ \diagdown\mathrm{NH_2}\end{matrix}\right]\mathrm{HCl}$$

Guanidine hydrochloride

It may be regarded as urea in which the oxygen is replaced by the divalent $=NH$ group (imino group). It also results from heating thiourea through the loss of hydrogen sulphide:

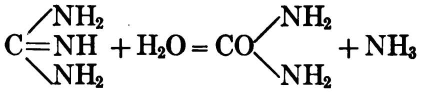
$$H_2N—C\boxed{S}—N\boxed{H_2} = NH_2—CN$$



$$\underset{\text{Cyanamide}}{NH_2—C\equiv N} + \underset{\text{Ammonium thiocyanate}}{NH_3 \cdot HCNS} = C\begin{matrix}\diagup NH_2\\ =NH\\ \diagdown NH_2\end{matrix} + HCNS$$

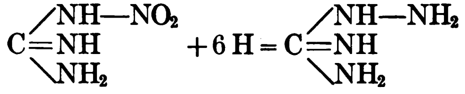
Guanidine is a colorless crystalline compound of a strongly basic character which absorbs moisture and carbon dioxide readily, forming a solution of guanidine carbonate, $[NH=C=(NH_2)_2]HCO_3$.

It is hydrolyzed by alkalies to urea and ammonia:



$$C\begin{matrix}\diagup NH_2\\ =NH\\ \diagdown NH_2\end{matrix} + H_2O = CO\begin{matrix}\diagup NH_2\\ \\ \diagdown NH_2\end{matrix} + NH_3$$

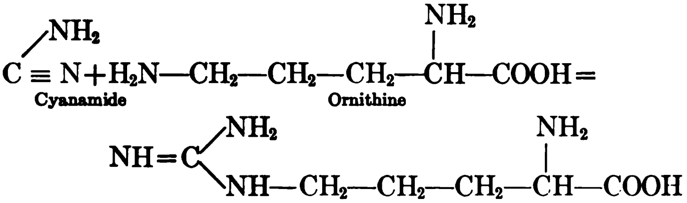
Guanidine reacts with strong nitric acid to form a nitro compound, *nitro guanidine*, which on reduction yields *amino guanidine:*



$$C\begin{matrix}\diagup NH—NO_2\\ =NH\\ \diagdown NH_2\end{matrix} + 6\,H = C\begin{matrix}\diagup NH—NH_2\\ =NH\\ \diagdown NH_2\end{matrix}$$

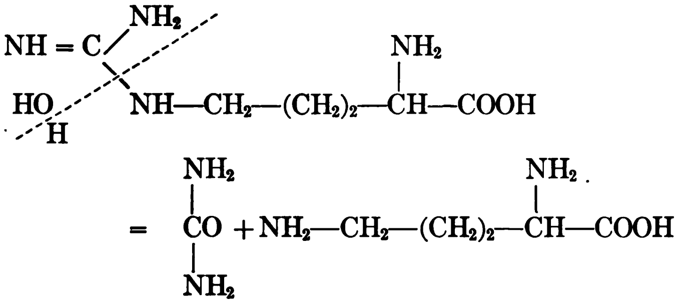
The latter is hydrolyzed by boiling with dilute acids or alkalies, forming hydrazine (**32**), carbon dioxide, and ammonia.

62. Arginine is an amino acid obtained by the hydrolysis of proteins by mineral acids. On hydrolysis by alkalies it is split up into urea and *ornithine,* an acid containing five carbon atoms and two amino groups, which is known by its behavior and synthesis to be α-δ-diamino valerianic acid (**71**). Furthermore arginine is synthesized by the condensation of cyanamide and ornithine:



α-amino-δ-guanidine valerianic acid (Arginine)

Its cleavage into urea and ornithine is illustrated by the reaction:

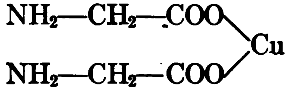


On vigorous treatment with alkalies the urea passes on into ammonia and carbon dioxide (**57**).

Arginine is a white crystalline compound which melts at 207.5° with decomposition. It is easily soluble in water, but insoluble in alcohol. It is precipitated by phosphotungstic acid, and by silver nitrate in the presence of barium hydroxide.

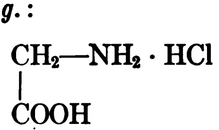
63. Aminoacetic Acid, glycine, glycocoll, $\overset{NH_2}{CH_2}—COOH$, is found in the free state in the adductor muscle of the scallop and in plant juices. It is a constituent of many proteins and is formed from these on hydrolysis by acids. It is the only amino acid derived from proteins which is certainly dispensable from the diet during growth. It plays an important rôle in the body as a protective substance, being condensed with several types of organic acids which are toxic, forming, with the separation of water, combinations which are of very much lower toxicity. An example of such a union is hippuric acid (see Hippuric Acid). Glycocoll is also a constituent of bile, where it exists combined with cholic acid as glycocholic acid.

Glycocoll is both an acid and base by reason of its carboxyl and amino groups, but these neutralize each other's effects so that its solutions react neutral to litmus, phenolphthalein, and certain other indicators. It forms salts with bases, the most important because of its tendency to crystallize being that with copper:



$$\begin{matrix} NH_2—CH_2—COO \\ NH_2—CH_2—COO \end{matrix} \!\!>\! Cu$$

This salt forms a deep blue solution. It likewise forms salts with acids, *e.g.*:



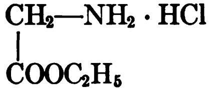
$$\begin{matrix} CH_2—NH_2 \cdot HCl \\ | \\ COOH \end{matrix}$$

Glycocoll chlorhydrate

These salts are crystalline, but are extremely soluble in water and are acid in reaction.

Of great importance in the isolation of glycocoll, as well as other amino acids, is the ethyl ester. It is formed by passing dry HCl gas into a suspension of the amino acid in absolute alcohol. As the hydrochloride is formed, it goes into solution and is then esterified. When the alcohol is evaporated the hydrochloride of the ester is obtained. From this, on treatment with strong sodium hydroxide, the ester is set free from the HCl and can be extracted with ether. All the esters of the amino acids are soluble in ether.

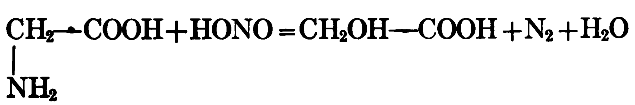
Glycocoll ester chlorhydrate is very sparingly soluble in absolute alcohol, which contains all the HCl gas which it can dissolve and crystallizes from such a solution to an extent approximating a quantitative separation. This principle has been utilized for its estimation and preparation.



$$\begin{array}{l} CH_2\text{—}NH_2 \cdot HCl \\ | \\ COOC_2H_5 \end{array}$$

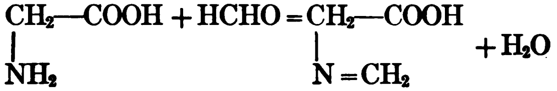
Glycocoll ester distills with some decomposition at ordinary pressures at 150°. Under diminished pressure it distills without decomposition.

With HNO_2 glycocoll, like other amino acids, decomposes with the formation of a hydroxy acid and elementary nitrogen.



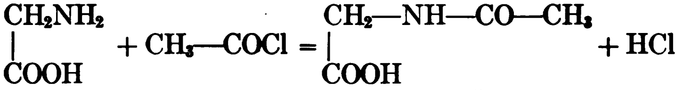
$$\begin{array}{l} CH_2\text{—}COOH + HONO = CH_2OH\text{—}COOH + N_2 + H_2O \\ | \\ NH_2 \end{array}$$

With formaldehyde its amino group condenses to form a methylene derivative which has no basic properties and can be sharply titrated with alkali and an indicator:



$$\begin{array}{l}CH_2{-}COOH\\ |\\ NH_2\end{array} + HCHO = \begin{array}{l}CH_2{-}COOH\\ |\\ N=CH_2\end{array} + H_2O$$

Amino acids, when treated with acid chlorides, yield *acetyl* derivatives of the following type:

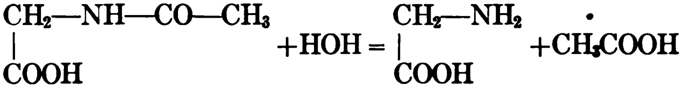


$$\begin{array}{l}CH_2NH_2\\ |\\ COOH\end{array} + CH_3{-}COCl = \begin{array}{l}CH_2{-}NH{-}CO{-}CH_3\\ |\\ COOH\end{array} + HCl$$

Acetyl glycocoll

Acetyl derivatives of the amines and amino acids are readily hydrolyzed into acetic acid and free amino group by boiling with dilute alkalies. Derivatives of this class can be formed by employing chlorides of other organic acids, as propionyl or butyryl chlorides. The groups are collectively known as *acyl* radicals, and the process of forming esters from alcohols and acid chlorides or amides from amines and acid chlorides is known as acylation.

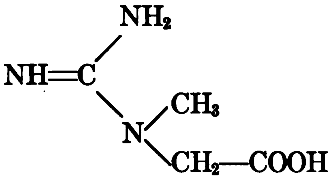
Acyl derivatives can frequently be purified much more satisfactorily, because of greater insolubility or greater tendency toward crystallization, than the alcohols or amines themselves, and are useful for the isolation and purification of many compounds, these being afterward regenerated by hydrolysis:



$$\begin{array}{l}CH_2{-}NH{-}CO{-}CH_3\\ |\\ COOH\end{array} + HOH = \begin{array}{l}CH_2{-}NH_2\\ |\\ COOH\end{array} + CH_3COOH$$

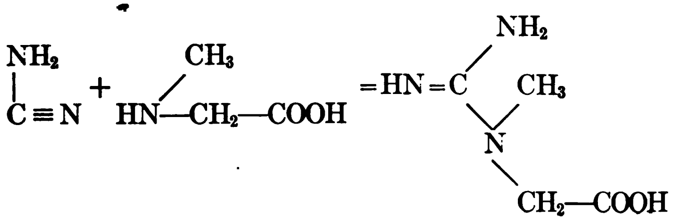
Of special value in the isolation and purification of various amino acids are the compounds analogous to the acyl derivatives, obtained from certain aromatic acids.

Creatine, methyl-guanidine acetic acid,

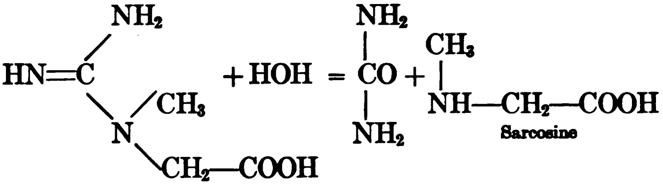


is found in muscle and organ tissues of vertebrates, but is not found in invertebrates. It is remarkably constant in amount, being found in human muscle to the extent of .39 per cent, and .52 per cent and .45 per cent respectively in the muscle of the rabbit and cat. It is not found in normal urine, but appears when carbohydrates are absent from the diet. It is not known how creatine is formed in the body.

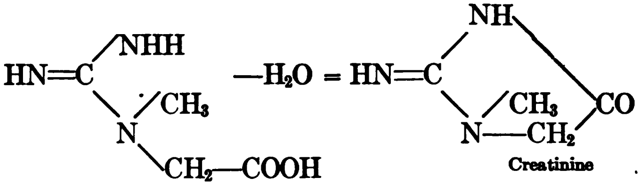
Creatine is a colorless crystalline compound with a bitter taste, which contains one molecule of water of crystallization which it loses at 100°. It is a base and forms salts with acids. It is formed synthetically by the condensation of cyanamide with methyl-amino acetic acid:



It is soluble in 74.4 parts of water at 10°; 100 cc. of 85 per cent alcohol at 17° dissolve .008 grams. On heating with alkalies it is hydrolyzed into urea and sarcosine or *methyl glycocoll.*



Creatinine is the *inner anhydride* of creatine. It is formed from creatine by boiling with mineral acids, which causes the abstraction of the elements of water:



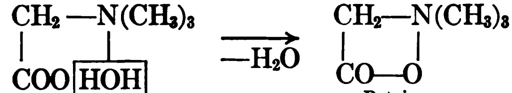
This compound is a never failing constituent of the urines of mammals. The daily excretion for man is .75 to 1.5 gram, and on diets free from creatine or creatinine the output is surprisingly constant and is independent of the intake of protein. Its precursor in the body is unknown.

Creatinine is soluble in 11.5 parts of cold water and more readily in hot. It dissolves in 625 parts of cold absolute alcohol. It is a stronger base than ammonia and displaces the latter from its salts. The most important salts are the potassium creatinine picrate,

$$C_4H_7ON_3 \cdot C_6H_3O_7N_3 \cdot C_6H_2O_7N_2K$$

and the zinc chloride double salt, $(C_4H_7ON_3)_2ZnCl_2$. The most important color reaction of creatinine is that with picric acid and sodium hydrate. The color closely resembles the deep orange of a solution of potassium dichromate.

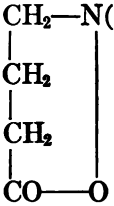
The Betaines. — These form a group of natural bases. The simplest member of the group is *betaine* or trimethyl glycocoll anhydride.



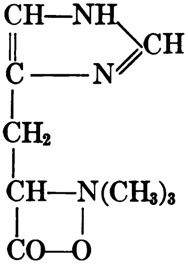
Trimethyl ammonium Acetic acid (hypothetical)

Betaine

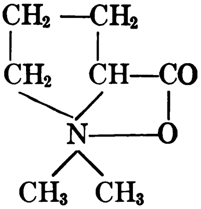
Its relation to the following bases is of interest:



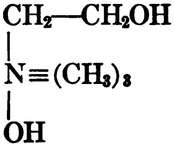
γ-*n*-butyro betaine



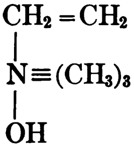
Trimethyl histidine betaine



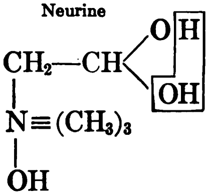
Stachydrine or Proline-betaine



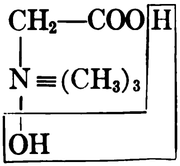
Choline



Neurine



Muscarine

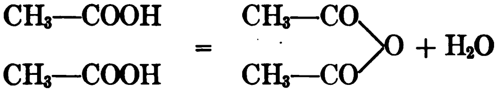


Betaine

The betaines are found in numerous plant extracts. Those from mushrooms and spores have been most investigated.

γ-n-butyro betaine has been isolated from putrid meat; *trimethyl histidine* and *muscarine* from mushroom extract; *stachydrine* from various plants; and *choline* and *neurine* from the brain, the latter only after decomposition.

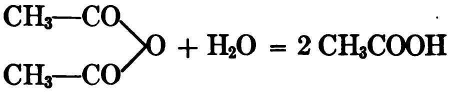
64. Acid Anhydrides.—There exists an important class of compounds which may be regarded as derived from two molecules of acid by the abstraction of a molecule of water. These are known as acid anhydrides:



$$\begin{array}{l} CH_3—COOH \\ CH_3—COOH \end{array} = \begin{array}{l} CH_3—CO \\ CH_3—CO \end{array}\!\!>O + H_2O$$

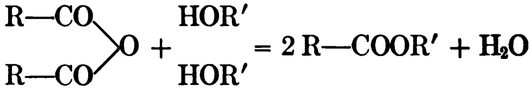
Acetic anhydride

Corresponding anhydrides of the other fatty acids are known. The lower members are liquids; those of higher molecular weight, solids of neutral reaction. The lower members react readily with water, regenerating the acids from which they were formed:



$$\begin{array}{l} CH_3—CO \\ CH_3—CO \end{array}\!\!>O + H_2O = 2\,CH_3COOH$$

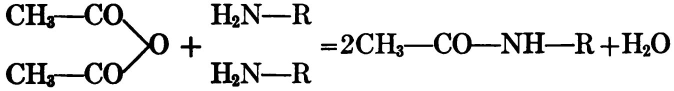
The higher members are much more stable toward water. Acid anhydrides react with alcohol to form esters in the sense of the following equation:



$$\begin{array}{l} R—CO \\ R—CO \end{array}\!\!>O + \begin{array}{l} HOR' \\ HOR' \end{array} = 2\,R—COOR' + H_2O$$

Acid anhydride Alcohol Ester

They are therefore useful in the same way as are the acyl chlorides for acylating alcohols. With primary and secondary amines they react, producing acyl derivatives:



$$\begin{matrix} CH_3\text{—}CO \\ CH_3\text{—}CO \end{matrix}\!\!>\!O + \begin{matrix} H_2N\text{—}R \\ H_2N\text{—}R \end{matrix} = 2CH_3\text{—}CO\text{—}NH\text{—}R + H_2O$$

Acetic anhydride, $(CH_3\text{—}CO)_2{=}O$, is the most important of the anhydrides of the fatty acids. It is a mobile liquid of suffocating odor, B.P. 137°, Sp. Gr. 1.073 at 20°. It is a reagent of great importance, being employed for the production of acyl derivatives.

65. Propionic Acid, $CH_3\text{—}CH_2\text{—}COOH$, the next homologue of acetic acid, is found in sweat and in mixtures resulting from the putrefaction of proteins by bacteria, where it is derived from certain amino acids by reactions which will be described later. It is formed from ethyl chloride through propionitrile, as an intermediate product:

$$(1)\quad CH_3\text{—}CH_2Cl + KCN = CH_3\text{—}CH_2\text{—}CN + KCl$$

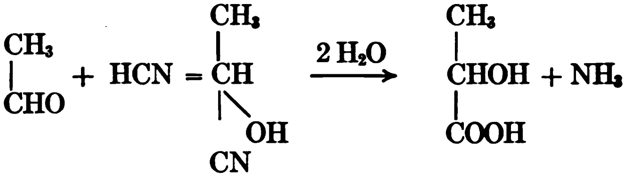
$$(2)\quad CH_3\text{—}CH_2CN + 2\,H_2O = CH_3\text{—}CH_2\text{—}COOH + NH_3$$

It is likewise formed by the oxidation of primary propyl alcohol:

$$CH_3\text{—}CH_2\text{—}CH_2OH + 3\,O = CH_3\text{—}CH_2\text{—}COOH + H_2O$$

This mode of formation makes clear its structure. It is a liquid with an odor which is suggestive of acetic acid, but is easily distinguishable from it. B.P. 140.7°. It is soluble in water in all proportions, but much less so in strong calcium chloride solutions. On adding this salt to its solutions it separates as an oil. Propionic acid is difficult to test for with certainty, since its properties are so closely similar to those of its immediate homologues, acetic and butyric acids. The silver salt contains 59.65 % of silver, and the barium salt 48.40 % of barium. The analysis of these salts, both of which are sparingly soluble in water, is the most convincing qualitatitive test.

α-chlor propionic acid, $CH_3—CHCl—COOH$, is formed by the direct action of chlorine upon propionic acid in the sunlight. The isomeric β-chlor derivative, $CH_2Cl—CH_2—COOH$, is likewise formed to some extent. The structure of these acids is made clear by other methods of formation; thus acetaldehyde adds hydrocyanic acid, forming hydroxy propionitrile:



$$\begin{array}{l}CH_3\\ |\\ CHO\end{array} + HCN = \begin{array}{l}CH_3\\ |\\ CH\\ |\diagdown\\ \quad OH\\ CN\end{array} \xrightarrow{2\,H_2O} \begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOH\end{array} + NH_3$$

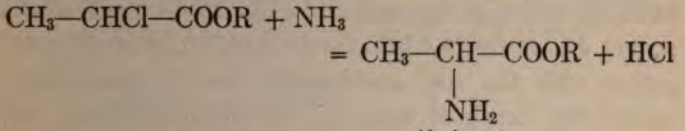
α-hydroxy propionic acid, or lactic acid, yields when treated with PCl_5 a product in which both the hydroxyl group of the carboxyl and that on the α-carbon atom are replaced by chlorine, viz.: α-chlor propionyl chloride, $CH_3—CHCl—COCl$. This, like acid chlorides in general, is decomposed by water, forming α-chlor propionic acid:

$$CH_3—CHCl—COCl + HOH = CH_3—CHCl—COOH + HCl$$

a-chlor propionic acid is of interest because it can be employed either for conversion into lactic acid or into *a*-amino-propionic acid, or alanine, one of the amino acids derived from proteins on hydrolysis:

$$CH_3—CHCl—COOR + AgOH = CH_3—CHOH—COOR + AgCl$$

Lactic acid ester



$$CH_3—CHCl—COOR + NH_3 = CH_3—\underset{\displaystyle NH_2}{\underset{|}{CH}}—COOR + HCl$$

Alanine ester

66. Lactic Acid, $CH_3—CHOH—COOH$, is the acid of sour milk. It is formed from milk sugar by the action of the lactic acid bacteria. Other sugars, as cane sugar, can likewise be used by this organism with the production of this acid. If a liter of 10% cane sugar solution be treated with 40 grams of calcium carbonate and 20–30 cc. of sour milk to supply the bacteria and the proteins, salts, etc., necessary for their multiplication, and the mixture kept at 37° for six to eight days, with occasional agitation, it will contain a considerable amount of calcium lactate. The solution is then boiled and evaporated to a small volume and cooled, when calcium lactate will crystallize out. On treating the crystals with sulphuric acid, calcium sulphate and free lactic acid are formed. The lactic acid can be extracted from the mixture by ether, in which it is readily soluble. On distilling off the ether lactic acid remains.

Lactic acid occurs in other fermented substances, such as sauerkraut and ensilage, in both cases arising through the agency of microörganisms. The conditions essential to the preservation of succulent vegetables and green fodders in these forms are close packing in an air-tight container from which the gases produced can escape. Rapid fermentation and respiration quickly remove the small amount of oxygen from the container, and through the catalytic action of enzymes in the plant cells a part of the sugars are converted into lactic acid. The acidity, together with the very considerable rise in temperature, causes the death of most of the microörganisms, and the material is preserved from putrefaction or further fermentation.

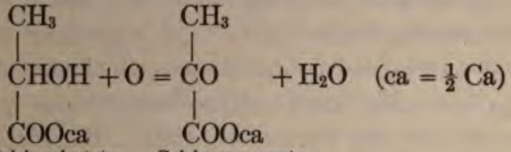
Lactic acid is a sirupy liquid which decomposes on distillation at ordinary atmospheric pressure, but can be distilled at about 85° if the pressure be reduced to .5 mm. of mercury. Distilled in this way, it crystallizes. The crystals are hygroscopic. It is readily soluble in water, alcohol, and ether, but insoluble in chloroform, carbon disulphide, or petroleum ether. It does not distill with steam. Lactic acid is decomposed when heated with dilute sulphuric acid into acetaldehyde and formic acid:

$$CH_3\text{—}CHOH\text{—}COOH = CH_3\text{—}CHO + HCOOH$$

According to certain investigators this reaction is catalyzed in the production of alcohol by fermentation, the formic acid being further decomposed into hydrogen and carbon dioxide, and the hydrogen serving to reduce the aldehyde to alcohol. (See Fermentation.) The most characteristic salt of lactic acid is the zinc salt,

$Zn(C_3H_5O_3)_2\ 3\ H_2O$. This is soluble in 52.5 parts of water at 15°. Lactic acid is frequently identified by the analysis of its zinc salt.

67. Pyruvic Acid, $CH_3—CO—COOH$. This acid is formed when calcium lactate is oxidized with potassium permanganate and by other more complicated reactions:



$$\begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOca\end{array} + O = \begin{array}{l}CH_3\\ |\\ CO\\ |\\ COOca\end{array} + H_2O \quad (ca = \tfrac{1}{2}\,Ca)$$

Calcium lactate Calcium pyruvate

It melts at 14° and boils at 61° under 12 mm. pressure. It is soluble in water, alcohol, and ether. Biochemical studies during recent years have made it highly probable that pyruvic acid is an intermediary product of the catabolism of carbohydrates, fats, and proteins (**164, 165**). An enzyme discovered by Neuberg in yeast has the property of decomposing pyruvic acid into acetaldehyde and carbon dioxide:

$$CH_3—CO—COOH \rightarrow CH_3—CHO + CO_2$$

Pyruvic acid can be reduced to lactic acid. Its relations to other compounds will be more fully discussed later (**164, 165**).

68. Stereoisomerism of the Lactic Acids. — In discussing the peculiar relationship between the chemical structure of the amyl alcohols and the property of rotating the ray of polarized light (**20**) it was pointed out that optical activity in amyl alcohol is associated with the presence of an *asymmetric carbon atom, i.e.* one whose four valences are bound each to a different radical or group. Lactic acid possesses a structure which conforms with the requirements of asymmetry, and we should therefore expect to find two kinds of lactic acid, having the same chemical properties and the same physical properties (specific gravity, boiling point, melting point, etc.) except in their behavior toward polarized light. This is actually the case.

There are two classes of substances which show optical activity. Some, like quartz and sodium chlorate, produce rotation only in the crystallized state. When they are dissolved or fused the optical property disappears. Others, like active amyl alcohol, lactic acid, oil of turpentine, camphor, and sugar, are optically active whether in the crystalline or in the liquid state, or in solution. In the former case the molecules themselves do not have an asymmetric structure, but they unite to form crystals which do. We may liken this to the construction of a spiral staircase, an asymmetrical structure from symmetrical bricks. When the staircase is again resolved into its component bricks, the asymmetry disappears. The optical activity of these substances depends therefore upon a peculiar arrangement of the molecules to form an asymmetric structure. In the case of compounds which are optically active in the liquid state, the asymmetry resides in the molecules themselves.

Ordinary lactic acid, obtained either by fermentation of milk or by synthesis, is optically inactive. There is in the normal muscle tissue of all higher animals, especially after activity, an appreciable amount of dextrorotatory lactic acid. The typhus bacillus and various vibrios ferment cane sugar with the formation of levorotatory lactic acid, and when these are mixed in equimolecular proportions there results the inactive acid identical with that obtained by synthesis or from fermented milk. Dextrolactic acid, from its presence in muscle, is called *sarcolactic acid.* It is present in muscle to the extent of .3–.5 parts per thousand. For brevity the two forms are written d- and l-lactic acids.

The reason for the difference in optical properties is best explained by the theory of Van't Hoff and Le Bel, who arrived at the same conclusions simultaneously and independently in 1874. The reasoning is briefly as follows:

The four affinities of the carbon atom are not to be conceived of as lying in the same plane, otherwise isomers should exist in compounds of the general type $Caabb$, where a and b represent atoms or radicals (**20**). No such isomerism has ever been observed. The simplest assumption that we can make with regard to the distribution in space of the four atoms or groups attached to the carbon atom is that the direction of each makes equal angles with the directions of the three others. This is equivalent to saying that the four atoms or groups are situated at the solid angles of a tetrahedron in the center of which the carbon atom itself is situated.

If the groups or atoms are all alike, they will be equally attracted by the carbon atom and the tetrahedron will be regular. If they are all different, the force with which each will be attracted will probably be different and they will arrange themselves at different distances from the carbon atom; the tetrahedron will then be irregular, *i.e.* it will have no plane of symmetry. Any compounds of the formula CH*abc* can exist in two forms called *enantiomorphs*, which are alike in the sense that an object is like its mirror image, but they will not be superposable.

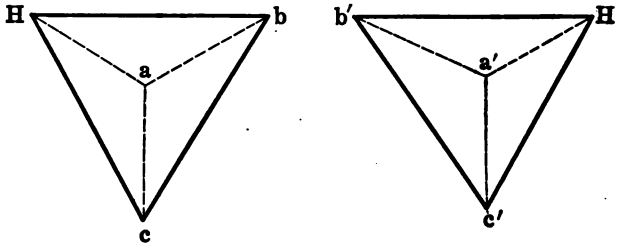


Fig. 11.

A consideration of Fig. 11 will help to make this clear: If we consider any group of three of the atoms or groups,

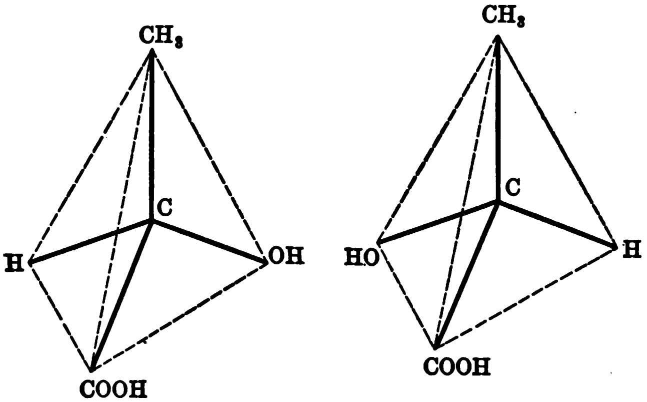


Fig. 12.

as H*bc*, looking toward the face about which they are arranged, any order as H*bc* which is clockwise in one figure will be counterclockwise in the other. If they are at different distances from the carbon atom, any continuous curve passing through the four atoms or groups in any given sequence will form a right-handed helix in one case and a left-handed helix in the other. Such a structure would account for the observed optical properties of such compounds. According to this conception the two active lactic acids can be represented by the stereo-chemical formulæ in Fig. 12:

There is a great difference in the biological values of the d- and l-lactic acids. When the mold *Penicillium glaucum* is grown upon a solution of ammonium lactate prepared from inactive fermentation lactic acid, and containing suitable inorganic salt additions, it is found after a time that the solution is dextrorotatory. The l- form is used up as a source of carbon by this mold, but not the d- form.

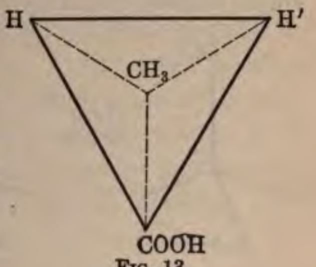


FIG. 13.

It has been already stated that synthetic lactic acid is inactive and consists of equal numbers of the d- and l-forms. A brief consideration will show that this must inevitably be the result. If in Fig. 13 we substitute one of the hydrogen atoms of propionic acid, H or H′, by some other element or radical, we must by the law of chance substitute H as frequently as H′, since in propionic acid there is a plane of symmetry from which H and H′ are equidistant, and any force which comes into play in the motions of the symmetric molecules of a gas or liquid which affects one of these hydrogen atoms, has an equal chance of affecting the other. In the synthesis of hydroxy propionitrile the same reasoning holds good. When hydrocyanic acid condenses with acetaldehyde, Fig. 14, the addition will take place as frequently according to one scheme as the other, and the acid resulting from the hydrolysis of the nitrile must be inactive.

The formation of inactive lactic acid in fermentation involves without doubt an addition of H and OH to an intermediary product of bacterial action in which the law of chance determines the positions which each radical takes. This will be further discussed in connection with fermentation (**164**).

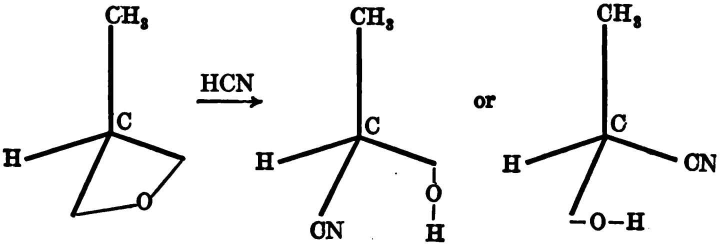


Fig. 14.

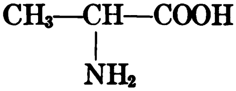
The production of l-lactic acid by certain organisms or the d-acid in the muscle tissues results from the cleavage of lactic acid from more complex compounds (sugars) which are themselves optically active and on which the positions of the H and OH groups are already determined in the molecule of the mother substance.

Lactic acid is decomposed by heating with sulphuric acid into acetaldehyde and formic acid:

$$CH_3—CHOH—COOH = CH_3—CHO + HCOOH$$

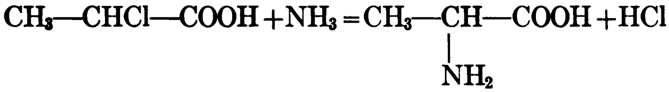
This decomposition is of interest because it shows the easiest line of cleavage of lactic acid. Acetaldehyde is without doubt formed from lactic acid in its decomposition by living tissues.

69. d-Alanine, *α*-aminopropionic acid,



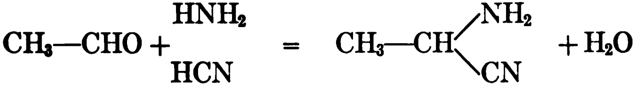
$$\underset{\displaystyle NH_2}{CH_3—\underset{|}{C}H—COOH}$$

is a constituent of the protein molecule and is formed on hydrolysis of the proteins by boiling with strong mineral acids. It is present in silk to the extent of over 20 %. It is formed, as are all the other amino acids found in proteins, by complete digestion of the latter with the enzymes, trypsin from the pancreas and erepsin from the mucous lining of the intestine. It is formed from *α*-chlor propionic acid on treatment with ammonia:

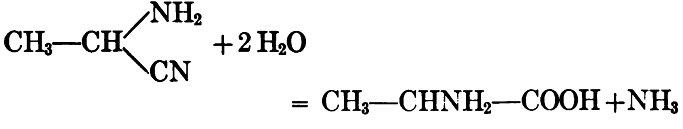


$$CH_3—CHCl—COOH + NH_3 = CH_3—\underset{\displaystyle NH_2}{\underset{|}{C}H}—COOH + HCl$$

Also by the interaction of acetaldehyde with ammonium cyanide:



$$CH_3—CHO + \begin{matrix} HNH_2 \\ HCN \end{matrix} = CH_3—CH\begin{matrix} ⁄NH_2 \\ \diagdown CN \end{matrix} + H_2O$$



$$CH_3—CH\begin{matrix} ⁄NH_2 \\ \diagdown CN \end{matrix} + 2\,H_2O$$
$$= CH_3—CHNH_2—COOH + NH_3$$

The reactions of alanine with chemical reagents are analogous to those of glycocoll (**63**). With nitrous acid it

[illegible]

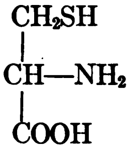
[illegible] long- [illegible] This [illegible] It is a remarkable fact that in the life processes of animals and plants, with but few exceptions, the compounds which play an important rôle are optically active, and but a single optical form occurs in nature. In no case can the optical antipode when synthesized in the laboratory be substituted for the naturally occurring form in biological processes.

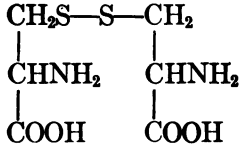
A remarkable transformation of one optical form of alanine into the other occurs when d-alanine is treated with nitrosyl bromide, and the resulting l-α-brom propionic acid is again converted into alanine by treatment with ammonia. With each repetition of these two transformations the alanine is changed from one optical form to the other. The following scheme will make this clear:

$$\begin{tikzcd}
\text{d-alanine} \arrow[d, "NOBr"] & \text{d-}\alpha\text{-brom propionic acid} \arrow[l, "NH_3"'] \\
\text{l-}\alpha\text{-brom propionic acid} \arrow[r, "NH_3"] & \text{l-alanine} \arrow[u, "NOBr"']
\end{tikzcd}$$

This is known from its discoverer as the "Walden transformation."

Alanine is a crystalline compound, soluble in 4.6 parts of water at 17°. It is nearly insoluble in alcohol. The ethyl ester can be distilled under diminished pressure without decomposition.

Cysteine, α-amino-β-thio lactic acid,  $\begin{array}{l} CH_2SH \\ | \\ CH—NH_2 \\ | \\ COOH \end{array}$, occurs as a constituent of certain proteins. It is the only derivative of proteins which yields sulphur. Cysteine is acted on by putrefactive bacteria, with the liberation of hydrogen sulphide and the formation of serine.



$$\begin{array}{lll} CH_2S & — S — & CH_2 \\ | & & | \\ CHNH_2 & & CHNH_2 \\ | & & | \\ COOH & & COOH \end{array}$$

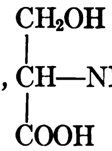
Cystine

Cystine forms large hexagonal plates, and can be identified by their characteristic appearance under the microscope.

Cystine is burned to carbon dioxide, water, ammonia, and sulphuric acid in the normal body, but there occurs an anomaly of metabolism in which this amino acid is regularly excreted in the urine — the condition of cystinuria.

The hydrogen sulphide of the digestive tract is derived from the action of microörganisms on cystine.

Serine, α-amino-β-hydroxy propionic acid,



$$\begin{array}{l} CH_2OH \\ | \\ CH\text{—}NH_2 \\ | \\ COOH \end{array}$$

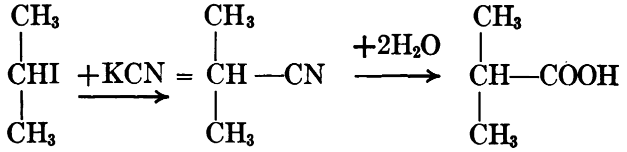
is another amino acid found among the products of the hydrolysis of the proteins. It is especially plentiful in silk. It is closely related to cystine, on the one hand, and to alanine, on the other.

70. Butyric Acid. — Two acids having the formula C_3H_7COOH are known. Normal butryic acid, $CH_3\text{—}CH_2\text{—}CH_2\text{—}COOH$, is formed from primary propyl iodide by the action of KCN and subsequent hydrolysis of the resulting nitrile:

$$CH_3\text{—}CH_2\text{—}CH_2I + KCN = CH_3\text{—}CH_2\text{—}CH_2\text{—}CN + KI$$

$$\begin{aligned} CH_3\text{—}CH_2\text{—}CH_2\text{—}CN &+ 2\,H_2O \\ &= CH_3\text{—}CH_2\text{—}CH_2\text{—}COOH + NH_3 \end{aligned}$$

Isobutyric acid is formed in a similar manner from secondary propyl iodide and KCN. It is therefore dimethyl acetic acid:



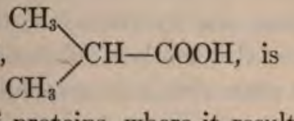
$$\begin{array}{l} CH_3 \\ | \\ CHI \\ | \\ CH_3 \end{array} \underset{\longrightarrow}{+KCN} = \begin{array}{l} CH_3 \\ | \\ CH\text{—}CN \\ | \\ CH_3 \end{array} \xrightarrow{+2H_2O} \begin{array}{l} CH_3 \\ | \\ CH\text{—}COOH \\ | \\ CH_3 \end{array}$$

Isobutyric acid

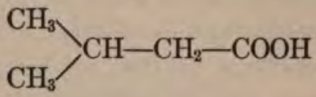
Normal butyric acid is found in butter, as the glycerin ester, to the extent of 2–4 %. Several kinds of microorganisms have been described (*e.g. B. butylicus*) which ferment sugars with the formation of butyric acid. All of these produce the normal acid. It is not produced in putrefaction. *B. hollobutyricus* can produce butyric acid from calcium lactate. The mechanism of this transformation can be discussed more satisfactorily after the properties of the unsaturated compounds have been treated (**164**). Normal butyric acid is a colorless, viscous liquid with a pungent, disagreeable, rancid odor. It is readily soluble in water, but is " salted out " by calcium chloride and other salts. It boils at 163°.

The calcium salt $(C_4H_7O_2)_2Ca \cdot H_2O$ is more soluble in cold than in hot water. This peculiar behavior is probably to be explained by the formation at low temperatures of a compound between the Ca salt and water whereby a *hydrate* is produced which is soluble. This is unstable at higher temperatures, so that on heating the higher hydrate disappears and the salt with the lower water content, being insoluble, separates out.

There is no α-amino butyric acid corresponding to glycocoll and alanine found in nature. In very dilute solutions (.2–1.%) and in the presence of suitable salts and a source of nitrogen, various molds, yeasts, and bacteria can employ butyric acid as a source of carbon. It is toxic, however, and possesses the property of paralyzing the motor nerve endings without interfering with the power of the muscle to contract.

71. Isobutyric Acid,  $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH\text{—}COOH$, is a product of the putrefaction of proteins, where it results from the decomposition of valin or α-amino isovalerianic acid (**73**). This isomer of normal butyric acid is not formed in fermentation of the sugars. Its odor is similar to that of *n*-butyric acid, but is not so offensive. It boils at 154° and, unlike its isomer, its calcium salt, is more soluble in hot water than in cold. No amino derivatives of isobutyric acid occur in nature. Its physiological and pharmacological properties closely resemble those of *n*-butyric acid.

72. Valerianic Acid, $CH_3—(CH_2)_3—COOH$. — Four isomers are possible. There are but two of these which are of biological importance, the most common one being *isovalerianic* or *isovaleric*, which is isopropylacetic acid:

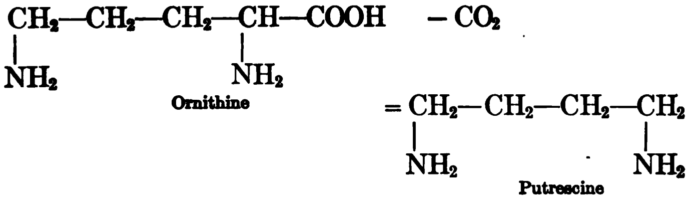


$$\begin{matrix}CH_3\diagdown \\ \quad CH—CH_2—COOH \\ CH_3\diagup\end{matrix}$$

It occurs in valerian root and in other plant juices, and among the putrefaction products of proteins, where it is derived from the amino acid *leucine* (**75**). It results from the oxidation of fermentation amyl alcohol. B. P. 175°. It has an odor like that of old cheese.

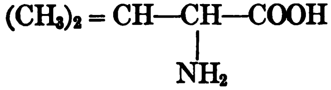
Bromine acts on isovaleric acid, forming α-brom isovaleric acid. M. P. 44°, B. P. 150° and 44 mm. pressure.

Ornithine, *α-δ-diamino valerianic acid,* does not occur in nature as such but is a cleavage product of arginine (**62**), resulting from the hydrolysis of the guanidine radical. Ornithine is the mother substance of tetramethylene diamine, or putrescine, a base found in putrefying protein mixtures.



$$\underset{\displaystyle NH_2}{CH_2}-CH_2-CH_2-\underset{\displaystyle NH_2}{CH}-COOH \quad - CO_2 = \underset{\displaystyle NH_2}{CH_2}-CH_2-CH_2-\underset{\displaystyle NH_2}{CH_2}$$

73. Amino Isovalerianic Acid, Valin,



$$(CH_3)_2 = CH-\underset{\displaystyle NH_2}{CH}-COOH$$

is one of the products resulting from the hydrolysis of proteins by acids or by the digestive enzymes. It is therefore of great biological importance. It is not present in large amounts in any protein; edestin, a globulin from the hemp seed, yields more than any other protein yet examined (5.6 %).

It has been prepared from sprouted lupine seeds, where it is formed by the digestion of the proteins of the seeds by proteolytic enzymes present in the germinating seeds. It has been produced synthetically by the action of ammonia on α-brom valeric acid, a method analogous to that by which amino acids in general are produced (**63**, **69**). The product of synthesis is optically inactive, while that obtained from proteins is d-valin. The synthetic amino acid can be resolved into its optical antipodes by a chemical method discovered by Pasteur. The principle of this method is as follows:

The d- and l- forms of optically active acids are exactly alike in configuration, being alike in the sense of an object and its mirror image, and have therefore the same physical properties (density, solubility, etc.) except as respects their influence upon polarized light (**20**). There are in many plants organic bases of complex constitution which contain in their molecules one or more asymmetric carbon atoms and are therefore capable of existing in optically active forms. As in the case of alanine and valin and other amino acids to be described later, there is found in nature only one optical variety, the other being incapable of playing any rôle in biological processes. Examples of such natural plant bases are quinine, strychnine, nicotine, etc.

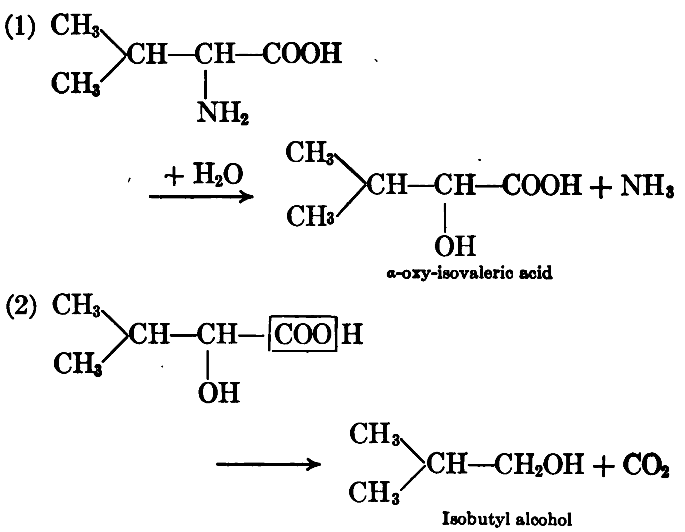
When now an inactive mixture of d- and l- acids is treated in solution with an optically active (*i.e.* asymmetrical) base, as strychnine, there are formed salts of the acid, *e.g.* d, l-valin, and base in the following combinations:

l-strychnine —— l-valin
l-strychnine —— d-valin

The salt molecules thus produced are no longer of the same structure and accordingly show different physical properties, as solubility, etc The form having the greater insolubility tends therefore to crystallize out first when the solution is concentrated by evaporation of a part of the solvent. After recrystallization of the salt it is decomposed by the addition of a stronger alkali to it in solution, when the very sparingly soluble strychnine crystallizes out, leaving the optically active acid in solution as a metallic salt. The mother liquor contains the more soluble isomer.

Mention has already been made of a second method of preparing one optical isomer from the inactive mixture which is based upon the ability of a living organism to use as food but one of the two forms (66). This method applies only to the preparation of that form which has no biological value.

Valin is the mother substance of isobutyl alcohol, as it is formed through the agency of yeast during fermentation. Yeast possesses the power to catalyze the following reactions:

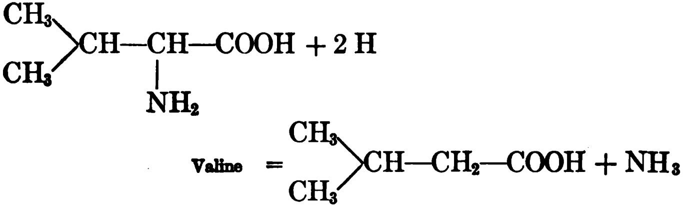


$$(1)\ (CH_3)_2CH{-}CH(NH_2){-}COOH \xrightarrow{+H_2O} (CH_3)_2CH{-}CH(OH){-}COOH + NH_3$$

$$(2)\ (CH_3)_2CH{-}CH(OH){-}\boxed{COO}H \longrightarrow (CH_3)_2CH{-}CH_2OH + CO_2$$

It is this type of decomposition of various amino acids which leads to the formation of fusel oil. Amyl alcohol has its origin in a similar manner from the amino acid leucine (75).

Under the influence of putrefactive bacteria (anaërobic conditions) the amino acids are deaminated, *i.e.* lose the amino group without losing the carboxyl group (decarboxylation).



$$\begin{matrix}\mathrm{CH_3} \\ \mathrm{CH_3}\end{matrix}\!\!>\mathrm{CH{-}\underset{\displaystyle NH_2}{\underset{|}{C}H}{-}COOH + 2\,H} = \begin{matrix}\mathrm{CH_3} \\ \mathrm{CH_3}\end{matrix}\!\!>\mathrm{CH{-}CH_2{-}COOH + NH_3}$$

Valine

Isovaleric acid

It is by this type of reaction that the valeric acid in feces and other putrefying mixtures is formed. The anaërobic organisms have the power of obtaining oxygen from certain organic compounds, and in so doing hydrogen becomes available in the nascent state, when it effects such reactions as that just described.

74. Caproic Acid, $\mathrm{CH_3(CH_2)_4{-}COOH}$. — The normal acid has been found in several plants, but it is of little biological importance. One of the isocaproic acids, isobutyl acetic,

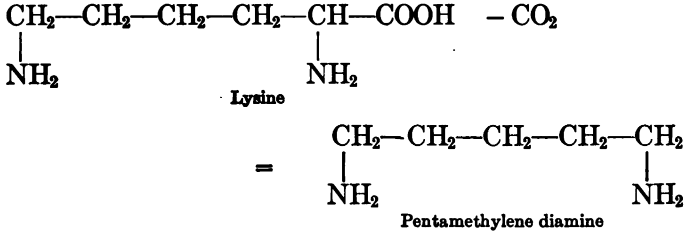
$$\mathrm{(CH_3)_2 = CH{-}CH_2{-}CH_2{-}COOH}$$

is contained in butter in the form of its glycerol ester. This isomer is of interest because one of its derivatives, viz., α-amino-isobutyl acetic acid, called for brevity *leucine*, is a regular constituent of the proteins, from which it results on hydrolysis.

Lysine, *α-ϵ-diamino caproic acid,* is one of the amino acids derived from the hydrolysis of proteins. It together with arginine (**62**) and histidine were formerly, and still to some extent are, designated as the "hexone bases" because they each contain six carbon atoms, and it was suspected that they played a special rôle in the formation of sugar from proteins in the body. This is now known not to be the case.

Lysine is a basic amino acid, and is precipitated along with the arginine and histidine by phosphotungstic acid. The three are collectively known as the diamino acids. This is not a fortunate name, since one of the three, histidine, contains but a single amino group.

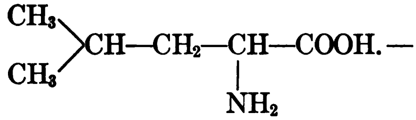
Putrefactive bacteria act on lysine, causing an elimination of carbon dioxide from the carboxyl group, forming pentamethylene diamine, *cadaverine*, which occurs in putrefying protein mixtures.

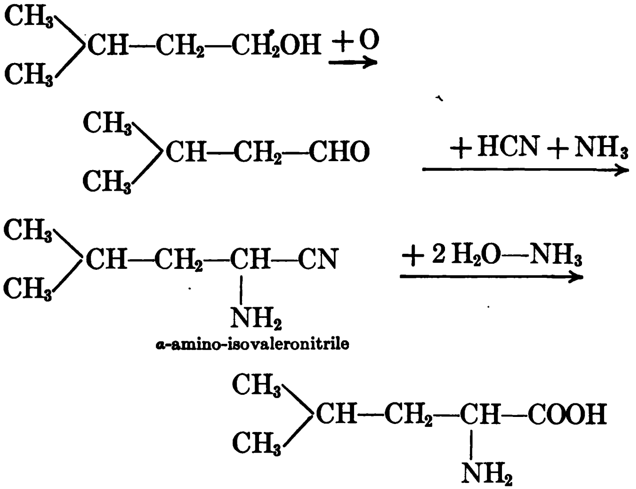


$$\underset{NH_2}{CH_2}-CH_2-CH_2-CH_2-\underset{NH_2}{CH}-COOH \; - CO_2 = \underset{NH_2}{CH_2}-CH_2-CH_2-CH_2-\underset{NH_2}{CH_2}$$

Lysine

Pentamethylene diamine

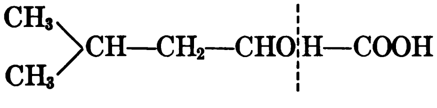
75. Leucine,  —Many proteins yield 10–20 % of this amino acid on hydrolysis. The l- form only occurs in nature. The structure of leucine is established by its synthesis from isoamyl alcohol. This is oxidized to the corresponding aldehyde, which is then condensed with hydrocyanic acid to form the α-oxynitrile of caproic acid. The latter reacts with ammonia with the replacement of the hydroxyl by an animo group. On hydrolysis of the nitrile to the corresponding acid inactive leucine results:



α-amino-isovaleronitrile

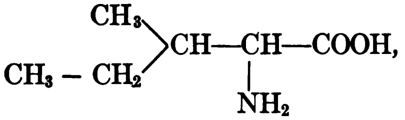
Leucine

Leucine is the mother substance of the inactive isoamyl alcohol of fermentation. The reactions by which it is probably formed were described under valin (**73**). It is not definitely established however whether or not the steps in the reaction involve the formation of isovaleraldehyde and formic acid:



and the subsequent reduction of the aldehyde to isoamyl alcohol. Such a course is in harmony with the well-known tendency of lactic acid to separate into acetaldehyde and formic acid (**66**).

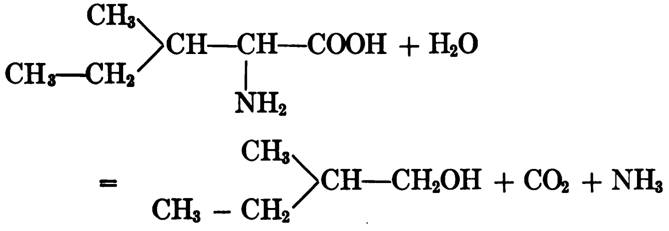
76. Isoleucine,



$$\begin{matrix} CH_3 \\ CH_3-CH_2 \end{matrix} \!\!> CH-\underset{\underset{NH_2}{|}}{C}H-COOH,$$

α-amino-methyl-ethyl propionic acid, has been isolated from beet molasses and from germinated peas, and occurs among the hydrolysis products of many proteins. Since so far as is known all of the amino acids found in proteins, with the single exception of glycocoll, are indispensable in the diet, all amino acids so derived are of the greatest interest and importance.

Isoleucine is, like leucine, used by yeasts as a source of nitrogen and energy. It undergoes cleavage into an optically active amyl alcohol, secondary butyl carbinol, by the loss of carbon dioxide and ammonia:



$$\begin{matrix} CH_3 \\ CH_3-CH_2 \end{matrix} \!\!> CH-\underset{\underset{NH_2}{|}}{C}H-COOH + H_2O$$

$$= \begin{matrix} CH_3 \\ CH_3-CH_2 \end{matrix} \!\!> CH-CH_2OH + CO_2 + NH_3$$

Putrefactive organisms change isoleucine into isocaproic acid, which is found in feces (**74**).

77. Higher Fatty Acids. — From C_6 upward only those members of the fatty acid series, $C_nH_{2n}O_2$, have any importance which contain an even number of carbon atoms. Those with an uneven number of C atoms either do not occur or are found but seldom and in traces. This remarkable fact has led to much speculation as to the mode of formation of the fatty acids in the plant and animal world, since any proposed series of chemical changes which lead to the building up of these acids in nature must, to constitute a tenable hypothesis, produce the even members only. Recently Miss Smedley of England has carried out synthetic work which throws much light on the mechanism of this synthesis. Its description must be deferred until certain other compounds are described (**165**).

The interest in the fatty acids from C_6 to C_{18} depends upon their great biological value as constituents of the fats. None of the fatty acids containing more than six C atoms are found in nature in the form of their amino derivatives. By definition *fats are the esters of the triatomic alcohol glycerol with the fatty acids*. Accordingly the ester of acetic or propionic acids would be classed chemically with the fats, although they do not have the characteristic physical properties of the fats, viz. a smooth, greasy feel, insolubility in water, and oily character when melted. The term fat usually signifies only those members of the series which possess the physical properties of fats. The names of the fats are derived from the name of the fatty acid with the ending -in substituted for -ic. Thus the triester of glycerol with formic acid is *triformin*; with acetic and butyric acid, *triacetin, tributyrin*, etc.

Since three esters are possible according as one, two, or three acid radicals are joined in ester formation with one molecule of glycerol, we distinguish mono-, di-, and tributyrin, caproin, etc.

The fatty acids which are of biological importance as components of fats are, beginning with C_4:

		M. P.
Butyric acid	$C_4H_8O_2$	-7.9°
Caproic acid	$C_6H_{12}O_2$	-1.5°
Caprylic acid	$C_8H_{16}O_2$	16.0°
Capric acid	$C_{10}H_{20}O_2$	31.4°
Lauric acid	$C_{12}H_{24}O_2$	43.6°
Myristic acid	$C_{14}H_{28}O_2$	53.8°
Palmitic acid	$C_{16}H_{32}O_2$	62.6°
Stearic acid	$C_{18}H_{36}O_2$	69.3°
Arachic acid	$C_{20}H_{40}O_2$	77.0°
Behenic acid	$C_{22}H_{44}O_2$	85.0°
Lignoceric acid	$C_{24}H_{48}O_2$	80.5°
Cerotic acid	$C_{26}H_{52}O_2$	——
Melissic acid	$C_{30}H_{60}O_2$	88.0°

The fatty acids above C_5 are very slightly soluble in water. One part of caprylic acid is dissolved in 400 parts of boiling water, but on cooling it separates almost completely in the crystalline form. The higher members are practically insoluble in water. They are more soluble in alcohol and dissolve readily in ether, chloroform, petroleum, ether, carbon tetrachloride, and in the volatile esters.

The most commonly occurring of the higher fatty acids are palmitic and stearic. They occur as esters of glycerol in both animals and plants. Their structure, as well as that of the lower members to C_6 which occur in nature, is shown by synthesis and by degradation to be *normal*. By a method analogous to the formation of the ketones

(**37**) the higher fatty acids are convertible into the lower members of the series.

Thus when barium stearate and barium acetate are subjected to dry distillation in a vacuum, barium carbonate and margaryl-methyl-ketone are produced:

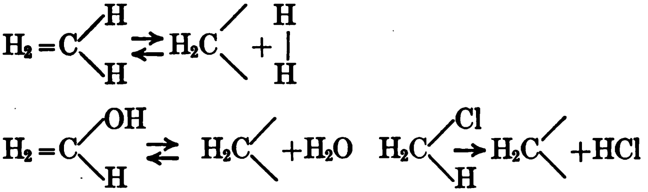
$$C_{17}H_{35}\boxed{COOba + baO}OCCH_3 = C_{17}H_{35}—CO—CH_3$$

On oxidation of the ketones the carbon chain is broken (**37**) and a fatty acid containing 17 carbon atoms, *margaric* acid, $C_{17}H_{35}O_2$, and acetic acids are formed. By repeating the ketone formation and oxidation as described the carbon chain has been shortened by CH_2 in successive steps with the formation successively of palmitic, myristic, lauric, and capric acids on each occasion when the product had an even number of carbon atoms. The acids up to capric have been synthesized by building up the carbon chain, *e.g.* by the formation of the nitrile from the primary halide of nonane, and hydrolysis of the nitrile to the corresponding acid.

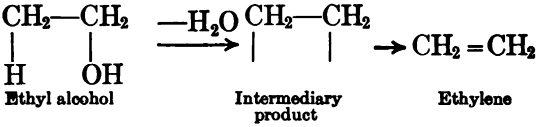
CHAPTER VII

THE UNSATURATED HYDROCARBONS

78. Alkylenes or Olefines, C_nH_{2n}. — When halogens react with the hydrocarbons of the paraffin series to form derivatives there is always formed one molecule of halogen acid, HCl or HBr, for each atom which enters the hydrocarbon in place of hydrogen. This is characteristic of *substitution reactions*. There is, however, another class of hydrocarbons which behave very differently toward chemical agents. When halogen comes into contact with the members of this series it is quickly absorbed or added to the molecule *without* the simultaneous formation of halogen hydride. Nascent hydrogen and the halogen acids are likewise absorbed by these hydrocarbons, the resulting compounds derived by hydrogen addition being identical with the hydrocarbons of the C_nH_{2n+2} series, and those formed by the absorption of halogen or halogen acids are identical with derivatives of the saturated hydrocarbons of the same composition, produced by substitution. Numerous efforts in the past to prepare a compound containing but one carbon atom and possessing the properties of the olefines have been unsuccessful. It has been already pointed out (**2**, **40**) that the occurrence of many reactions of compounds containing carbon can best be explained on the assumption that very small amounts of the radical methylene $CH_2=$ exist in dynamic equilibrium with molecules of different types. Thus the reactivity of methane, methyl alcohol, and methyl chloride depends upon the fact that each contains a relatively small per cent of *active methylene particles* at ordinary temperatures:

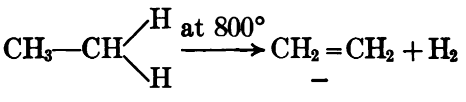


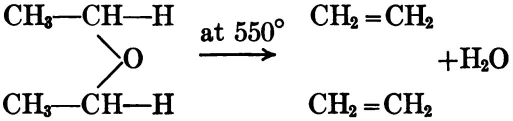
79. Ethylene, $CH_2=CH_2$.—When ethyl alcohol is acted upon by concentrated sulphuric acid or zinc chloride, powerful dehydrating agents, water is abstracted from the molecule and the simplest of the olefines, *ethylene,* is formed. The same change is effected by heating ethyl alcohol alone to 650°. It separates into ethylene and water:

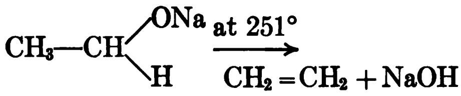


$$\underset{\text{H}}{\underset{|}{CH_2}}—\underset{\text{OH}}{\underset{|}{CH_2}} \xrightarrow{-H_2O} \underset{|}{CH_2}—\underset{|}{CH_2} \rightarrow CH_2=CH_2$$

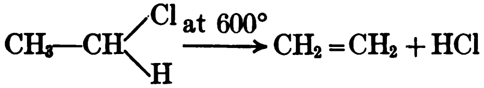
Further instances of the formation of ethylene by dissociation are the following:

Ethane 

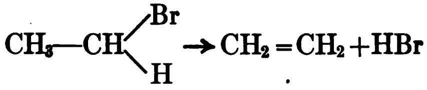
Ethyl ether 

Sodium ethylate 

$$CH_3{-}CH\begin{matrix}\diagup ONa\\ \diagdown H\end{matrix}\xrightarrow{\text{at } 251^\circ} CH_2{=}CH_2+NaOH$$

Ethyl chloride 

$$CH_3{-}CH\begin{matrix}\diagup Cl\\ \diagdown H\end{matrix}\xrightarrow{\text{at } 600^\circ} CH_2{=}CH_2+HCl$$

Ethyl bromide 

$$CH_3{-}CH\begin{matrix}\diagup Br\\ \diagdown H\end{matrix}\rightarrow CH_2{=}CH_2+HBr$$

All the above decompositions take place at the temperatures named and the products on cooling do not recombine. Ethylene can therefore be obtained quantitatively by passing, *e.g.*, ethyl chloride or bromide through a tube heated to the decomposition point.

The assumption is made that two carbon atoms in the olefines are bound together by a double bond. Adhering to the theory that in methane and its substitution products the carbon atom occupies the central position in a molecule in which the four attractive forces are directed so as to make equal angles with one another, *i.e.* as toward the four solid angles of a tetrahedron, the structures assigned to ethane and ethylene are as follows:

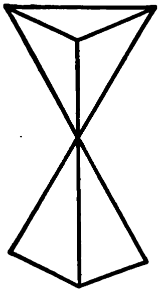


Fig. 15.

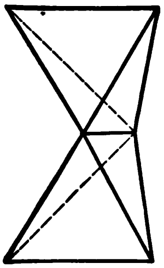


Fig. 16.

The double bond does not bind the C atoms in a more stable union than the single bond. On the contrary, as has been stated, there is a pronounced tendency for the double bond to absorb with avidity atoms or groups and to pass into a "saturated" condition. Compounds containing the double bond, are, because of this property, spoken of as "unsaturated" compounds. The unsaturated compounds are given the ending *ene* preceded by the name of the alkyl radical from which they are derived. This high reactivity of the olefines is doubtless due to the existence of a considerable amount of dissociated particles $R-\underset{|}{C}H-\underset{|}{C}H-R$ along with the form represented by Figure 16, for the double bond. These are in dynamic equilibrium with the undissociated form, and when compounds capable of absorption become available, the dissociated particles are rapidly removed and more double bonds dissociate until the reaction is complete:

$$CH_2=CH_2 \leftrightarrows \underset{|}{C}H_2-\underset{|}{C}H_2 \xrightarrow{+2R} CH_2R-CH_2R$$

Another method of preparing ethylene and its homologues confirms the hypothesis advanced concerning its structure. Thus ethyl iodide, when treated with aqueous KOH, yields ethyl alcohol. With alcoholic KOH solution it yields ethylene:

$$CH_3-CH_2I+\underset{\text{Aqueous}}{KOH} = CH_3-CH_2-OH+KI$$

$$CH_3-CH_2I+\underset{\text{Alcoholic}}{KOH} = CH_2=CH_2+KI+H_2O$$

When ethylene is mixed with hydrogen and passed over finely divided nickel heated to 300°, addition of hydrogen atoms takes place and ethane is formed:

$$CH_2 = CH_2 + H_2 = CH_3—CH_3$$

In a similar manner halogen acids are absorbed by the olefines with the formation of halogen derivatives of the paraffins:

$$CH_2 = CH_2 + HI = CH_3—CH_2I$$

This reaction takes place with moderate speed at about the boiling point of water, but HBr reacts much more slowly than hydriodic acid and HCl does not react at all. This finds its explanation in the fact that the acid as a molecule is not added by the olefine, but its constituent atoms; HI is an easily dissociated acid, readily liberating iodine, in the presence of even feeble oxidizing agents; while HCl is a very stable acid. HBr is intermediate in its stability. Since the bond between H and Cl must be broken before addition can take place, the firm union in HCl prevents its reaction.

The olefines are much more easily oxidized than are the saturated compounds. While ethane is not oxidized by potassium permanganate or chromic acid, the olefines are readily attacked. Dilute permanganate oxidizes ethylene to ethylene glycol:

$$CH_2 = CH_2 + HOH + O = CH_2OH—CH_2OH$$

The decolorization of dilute permanganate solution serves to detect unsaturated compounds in a mixture of hydrocarbons.

91. Propylidene Compounds.—It has already been pointed out (26), that the chlorides of phosphorus react with aldehydes and ketones with the replacement of the oxygen of the carbonyl group CO by two chlorine atoms $\underset{|}{C}=Cl_2$. Thus propyl aldehyde yields propylidene chloride:

$$CH_3\text{—}CH_2\text{—}CHCl_2$$

and acetone yields dichloracetone:

$$CH_3\text{—}CCl_2\text{—}CH_3$$

On removing one molecule of haloid acid from compounds of these types there result two isomeric chlor propylenes, having chlorine linked to a doubly linked carbon atom.

$$\underset{\text{Propylidene chloride}}{CH_3\text{—}CH_2\text{—}CHCl_2} \xrightarrow{\text{—}HCl} \underset{\alpha\text{-chlor propylene}}{CH_3\text{—}CH=CHCl}$$

$$\underset{\text{Chloracetone}}{CH_3\ \ CCl_2\text{—}CH_3} \xrightarrow{\text{—}HCl} \underset{\beta\text{-chlor propylene}}{CH_3\text{—}CCl=CH_2}$$

This type of halogen compound differs markedly from the alkyl halides in which the halogen is linked to a carbon atom having only single bonds. While in the alkyl halides the halogen is readily replaceable by hydroxyl, alkyl, amino groups, etc., this property is almost wholly wanting in compounds whose halogen is linked to carbon with a double bond. They do not react with alkalies to produce alcohols nor with sodium ethylate to produce ethers. Instead there are formed compounds which are substitution products of the triple bond hydrocarbons, the *acetylenes* (**83**). From $CH_3—CCl_2—CH_3$ by the abstraction of two HCl there never results a diolefine $CH_2 = C = .CH_2$, as might be expected.

An isomer of *a*- and *β*-chlor propylene is known as allyl chloride, $CH_2 = CH—CH_2Cl$. This reacts just as do alkyl halides, notwithstanding the presence of the double bond in the molecule. Thus with KOH it yields allyl alcohol:

$$CH_2 = CH—CH_2Cl + KOH = CH_2 = CH—CH_2OH + KCl$$

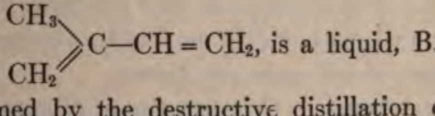
This alcohol will be described later (**85**).

82. The Diolefines. — Compounds containing two double bonds are known which have considerable importance. *Allene*, $CH_2 = C = CH_2$, is a gaseous hydrocarbon which can be prepared from tribrom propane by the abstraction of one molecule of HBr by means of alcoholic KOH, and the subsequent removal of the remaining two bromine atoms by zinc dust:

$$CH_2Br—CHBr—CH_2Br \xrightarrow{—HBr} \underset{\text{Dibrom propylene}}{CH_2 = CBr—CH_2Br}$$

$$\xrightarrow{—2\,Br} CH_2 = C = CH_2$$

It is a colorless gas.

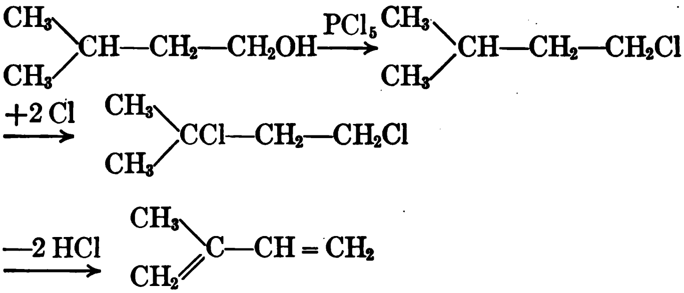
Isoprene, 

$$\begin{matrix} CH_3 \\ CH_2 \end{matrix}\!\!>\!C—CH = CH_2$$

, is a liquid, B. P. 37°.

It is formed by the destructive distillation of India rubber, and also by passing turpentine through a tube heated to redness. On treatment with acids it polymerizes, forming rubber again.

It is also formed from isobutyl carbinol, one of the amyl alcohols, by the following series of transformations:

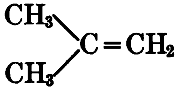


$$(CH_3)_2CH—CH_2—CH_2OH \xrightarrow{PCl_5} (CH_3)_2CH—CH_2—CH_2Cl \xrightarrow{+2\,Cl} (CH_3)_2CCl—CH_2—CH_2Cl \xrightarrow{—2\,HCl} \begin{matrix} CH_3 \\ CH_2 \end{matrix}\!\!>\!C—CH=CH_2$$

In the presence of metallic sodium it polymerizes to a product having the physical properties of rubber, but not identical with it chemically.

Butylenes. — Three butylenes are known, and this number only is theoretically possible.

$CH_3—CH_2—CH=CH_2$

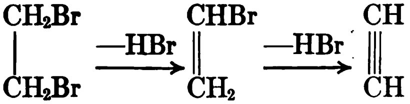


$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C=CH_2$$

$CH_3—CH=CH—CH_3$

They are prepared by methods analogous to propylene. They differ from ethylene in their tendency to polymerize when treated with H_2SO_4 or $ZnCl_2$. Numerous higher homologues of this series are known.

83. Acetylenes. — On treatment of dibrom ethane with alcoholic KOH two molecules of HBr are abstracted with the formation of a still more highly unsaturated compound *acetylene*:



$$\begin{array}{c} CH_2Br \\ | \\ CH_2Br \end{array} \xrightarrow{-HBr} \begin{array}{c} CHBr \\ \| \\ CH_2 \end{array} \xrightarrow{-HBr} \begin{array}{c} CH \\ \equiv \\ CH \end{array}$$

Dibrom ethane Vinyl bromide Acetylene

Acetylene is a gas which shows all the properties of the olefines, but is more unsaturated and reacts with two molecules of halogen acid, four halogen atoms, etc. In conformity with the theory of the tetrahedral structure of the methane molecule the structure of the triple bond hydrocarbons is to be represented as in Figure 17. The carbon atoms united by a double bond possess less freedom of movement with respect to each other than those united by a single bond, and two united by a triple bond possess still less freedom of movement with respect to each other. This conception is in harmony with a special type of isomerism which is shown by compounds having the double bond as contrasted with those in which no double bond is present. That carbon atoms which are doubly and triply bound are under a strain, which leads to their tendency to change from the unstable state into other forms is further indicated by the heats of formation and of combustion of ethane, ethylene, and acetylene:

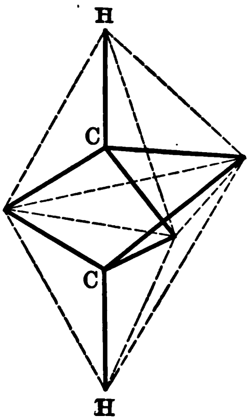


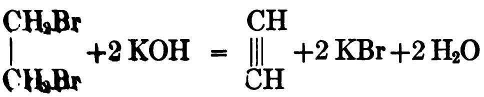
Fig. 17.

	HEAT OF COMBUSTION	HEAT OF FORMATION
Ethane	372.3 Cal.	23.3 Cal.
Ethylene	341.1 Cal.	-14.6 Cal.
Acetylene	313.8 Cal.	-51.5 Cal.

Whereas ethane is formed from its elements with the liberation of 23.3 Cal. of heat for each gram molecule, energy must be supplied to induce the formation of the double bond and still more to form the triple bond. We may liken the formation of these unsaturated compounds to the bending of a bow into a position of tension. While under a strain and possessing stored up energy it has a strong tendency to change to a body of a new conformation.

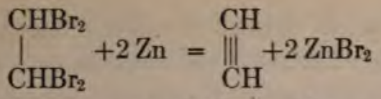
When placed under pressure greater than two atmospheres, acetylene is readily exploded by a shock. The change which takes place is one of *polymerization,* three molecules uniting to form one molecule of *benzene.* The nature of this change will be treated later (**166**).

Preparation.—Acetylene is formed from ethylene bromide by the abstraction of two molecules of HBr. This is readily effected by heating with alcoholic KOH:



$$\begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix} + 2\,KOH = \begin{matrix} CH \\ ||| \\ CH \end{matrix} + 2\,KBr + 2\,H_2O$$

Metallic zinc abstracts bromine from tetrabrom ethane in alcoholic solution, with the formation of acetylene:



$$\begin{array}{c} CHBr_2 \\ | \\ CHBr_2 \end{array} + 2\,Zn = \begin{array}{c} CH \\ ||| \\ CH \end{array} + 2\,ZnBr_2$$

A characteristic property of hydrocarbons containing the group $HC\equiv$ is the formation of insoluble metallic compounds of the composition C_2Ag_2 and C_2Cu_2, silver and cuprous acetylides respectively, when acetylene or its *monoalkyl derivatives* are passed into an ammoniacal solution of silver nitrate or of cuprous chloride. This property is utilized in analytical work to determine the acetylene content of a mixture. The quantitative capacity to absorb bromine serves as an estimation of the total unsaturated group (olefines and acetylenes), and the amount of metallic derivative forms a basis for the calculation of the content of doubly and triply unsaturated hydrocarbons in the mixture. These compounds are highly explosive when dry. They are decomposed by hydrochloric acid with the regeneration of acetylene:

$$C_2Ag_2 + 2\,HCl = CH \equiv CH + 2\,AgCl$$

Derivatives of acetylene in which both hydrogen atoms are substituted by alkyl groups do not form these metallic compounds. Acetylene is most conveniently prepared by treating calcium carbide with water. When lime and carbon (coal) are heated together in an electric furnace, the calcium oxide is reduced and calcium and carbon combine to form calcium acetylide, commonly called *calcium carbide*, C_2Ca. This compound reacts with water somewhat violently with the evolution of considerable heat and the formation of acetylene:

$$C_2Ca + 2\,H_2O = CH \equiv CH + Ca(OH)_2$$

When liberated through a suitable burner, acetylene burns with an intensely luminous flame. Its mixtures with air are much more dangerously explosive than are mixtures of air and coal gas, due to the reactive properties of the acetylene as compared with the paraffin hydrocarbons, and also to the wide limits of composition of air and acetylene which form explosive mixtures. Mixtures containing 3 to 82 per cent of acetylene are explosive, while the limits for coal gas are only 5 to 28 per cent. In addition the velocity of propagation of the reaction between oxygen (of the air) and acetylene is much greater in the case of the acetylene mixture, which intensifies the force of explosion.

The carbides of certain other metals yield hydrocarbons other than acetylene. Aluminum carbide yields methane on decomposition by water. Uranium carbide yields mixtures of methane and of liquid and solid hydrocarbons.

Acetylene, $CH\equiv CH$, is a gas of unpleasant odor. One volume of water dissolves about 1 volume of the gas; benzene and alcohol dissolve 4 and 6 volumes respectively, at ordinary temperatures; while acetone, which is the best solvent, dissolves 25 volumes, and much greater quantities under pressure.

It can be synthesized from its elements by passing an electric spark between carbon poles in an atmosphere of hydrogen, a small amount of methane and ethane being simultaneously produced. It is produced in small amount when many organic substances are subjected to incomplete combustion.

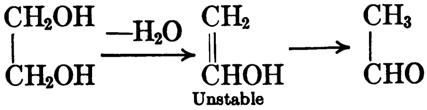
Acetylene is more poisonous than ethane or ethylene. A content of one volume per cent of the gas in air produces narcosis with failure of the heart and of respiration. Higher homologues of acetylene in which the hydrogen atoms are replaced by alkyl groups are likewise known.

SUBSTITUTION PRODUCTS OF THE UNSATURATED HYDROCARBONS

84. Vinyl Alcohol, $CH_2=CHOH$, has never been isolated and its existence is uncertain. When vinyl bromide is treated with KOH we should expect the formation of an alcohol of this type, but a rearrangement of atoms takes place with the disappearance of the double bond between the carbon atoms. When vinyl alcohol is to be expected, acetaldehyde is obtained:

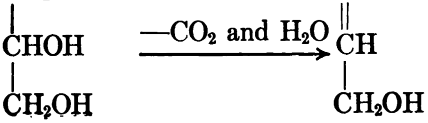
$$CH_2=CHBr+KOH=\underset{\text{Unstable}}{CH_2{=}CHOH}\rightarrow CH_3{-}CHO+KBr$$

In a similar manner the abstraction of water from glycol leads to the formation of acetaldehyde and not vinyl alcohol:



$$\begin{array}{c}CH_2OH\\ |\\ CH_2OH\end{array}\xrightarrow{-H_2O}\underset{\text{Unstable}}{\begin{array}{c}CH_2\\ \|\\ CHOH\end{array}}\longrightarrow\begin{array}{c}CH_3\\ |\\ CHO\end{array}$$

85. Allyl Alcohol, $CH_2=CH{-}CH_2OH$, is best prepared from the monoformic ester of glycerol or *monoformin:*



$$\begin{array}{c}CH_2OOCH\\ |\\ CHOH\\ |\\ CH_2OH\end{array}\xrightarrow{-CO_2\text{ and }H_2O}\begin{array}{c}CH_2\\ \|\\ CH\\ |\\ CH_2OH\end{array}$$

The structure of this compound is made clear by the following behavior:

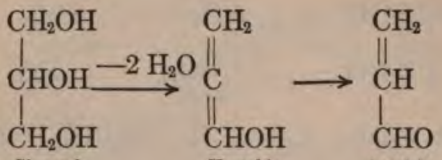
(1) It behaves like an alcohol in reacting with sodium with the evolution of hydrogen.

(2) It yields an *acetyl derivative* when treated with acetyl chloride.

(3) With nascent hydrogen ($Zn + H_2SO_4$) it is converted into normal propyl alcohol. This shows that the alcohol radical is attached to an end carbon atom and is therefore a primary alcohol.

(4) The evidence that it is a primary alcohol is supported by the fact that it yields an aldehyde and an acid containing the same number of carbon atoms as the alcohol itself.

Acrylic Aldehyde, Acrolein, $CH_2{=}CH{-}CHO$, is best prepared by the abstraction of two molecules of water from glycerol. This is best effected by heating with potassium bisulphate. The reaction which takes place is probably the following:



$$\begin{array}{ccccc}
CH_2OH & & CH_2 & & CH_2 \\
| & & \| & & \| \\
CHOH & \xrightarrow{-2\,H_2O} & C & \longrightarrow & CH \\
| & & \| & & | \\
CH_2OH & & CHOH & & CHO \\
\text{Glycerol} & & \text{Unstable} & & \text{Acrolein}
\end{array}$$

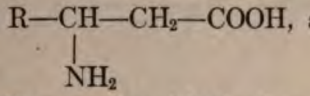
This behavior is in agreement with experience which, as pointed out above, leads to rearrangement of the atoms with the formation of an aldehyde whenever we should expect the formation of an alcohol group in union with a doubly linked carbon atom (**84**).

Allyl alcohol is found as an ester in the form of allyl iso-thio-cyanate, C_3H_5NCS, in the seeds of mustard. It is not free but combined with glucose as a glucoside (**161**).

Allyl Sulphide, $(C_3H_5)_2S$, is the principal constituent of oil of garlic.

Acrylic aldehyde, or *acrolein*, can in turn be oxidized to the corresponding acid, acrylic acid:

$$CH_2=CH—CHO+O=\underset{\text{Acrylic acid}}{CH_2=CH—COOH}$$

β-Amino Acids,  $R—\underset{\displaystyle NH_2}{\underset{|}{CH}}—CH_2—COOH$, are unstable and readily split off ammonia with the formation of unsaturated compounds. Thus β-iodopropionic acid yields with ammonia β-aminopropionic acid which splits off ammonia, forming acrylic acid.

86. Acids of the Oleic Series, $C_nH_{2n-2}O_2$. — The first member of this series of acids, which differ from the saturated fatty acids by having one double bond, is acrylic acid. The second member, *methyl acrylic acid*, is known as crotonic acid. It is formed by the action of dehydrating agents upon β-oxy-butyric acid. The latter compound is formed directly by the condensation of two molecules of acetaldehyde by the " aldol condensation " (**32, 124**):

$$CH_3—CHOH—CH_2—COOH \xrightarrow{—H_2O} CH_3—CH=CH—COOH.$$

This acid occurs in croton oil. It is a crystalline substance which melts at 72° and boils at 180°. At 19° it is soluble in 12.5 parts of water.

There is however an *isocrotonic* acid which is an oil which boils at 172° and when maintained for a time at a temperature of 170–180 goes over into crotonic acid. Both of these acids yield normal butyric acid on treatment with nascent hydrogen and have, therefore, the normal carbon chain. They exhibit a kind of isomerism which cannot be explained by the ordinary constitutional formulæ. This type of isomerism, which is peculiar to the ethylene compounds, is the necessary result of the restriction of motion of two carbon atoms linked by a double bond. Thus butyric acid may be represented as in Figure 18.

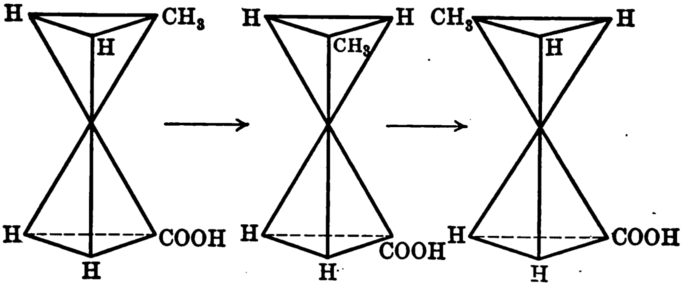
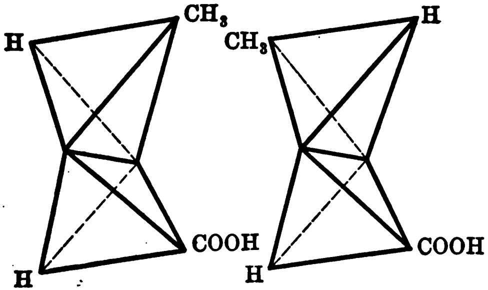


FIG. 18.

The system of the carbon atom at the center of the upper tetrahedron and its three combined atoms or groups should have no restriction as to the relative positions which they may assume with respect to the carbon atom at the center of the lower tetrahedron and its system of atoms and groups. Each should be free to rotate freely about their common axis, and all the possible arrangements probably occur; and because all are constantly shifting, one into every other possible position, there is but one normal butyric acid.

When, as in crotonic acid, we establish the double bond (Fig. 19), the two carbon atoms affected by the double bond lose their freedom of rotating about a common axis independently of each other, and we should expect different physical properties to result from these two different structures. This type of isomerism will be more fully dealt with in connection with maleic and fumaric acids (**133**). Since a considerable number of compounds of this class have been studied, in many of which it is easier to decide which compound represents the *cis* and which the *trans* form, the following generalizations may be made: The acid having the *cis* form is much the more soluble; it has also the lower melting point, and in the case of the monobasic acids is the stronger acid of the two (more highly dissociated).



Cis form *Trans* form

FIG. 19. — CROTONIC ACIDS.

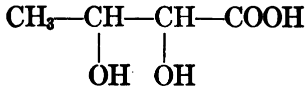
In addition to the two isomers of crotonic acid just described, two other acids of the same formula are known, that represented by crotonic and isocrotonic acid. Oleic acid represents the *cis* and elaidic acid the *trans* form.

The position of the double bond in oleic acid is established by the fact that when compounds containing this linkage are oxidized, the oxidation takes place at the point of unsaturation; thus:

$$\underset{\text{Crotonic acid}}{CH_3—CH=\vdots CH—COOH} \xrightarrow{+4O} \underset{\text{Acetic acid}}{CH_3—COOH} + \underset{\text{Oxalic acid}}{HOOC—COOH}$$

$$\underset{\text{Acrylic acid}}{CH_2=CH—COOH} \xrightarrow{+4O} \underset{\text{Formic acid}}{HCOOH} + HOOC—COOH$$

the oxidation in all such cases leads first to the formation of two secondary alcohol groups:



$$CH_3—\underset{\displaystyle OH}{\underset{|}{CH}}—\underset{\displaystyle OH}{\underset{|}{CH}}—COOH$$

then a separation of the carbon chain. Thus oleic acid when oxidized with a dilute solution of potassium permanganate yields, first dihydroxy stearic acid, then *pelargonic* acid, $CH_3—(CH_2)_7—COOH$, and *azeliac* acid, $COOH—(CH_2)_7—COOH$. From this evidence it is concluded that the double bond in oleic acid is at the middle of the chain, *i.e.* between the ninth and tenth carbon atoms.

88. Acids with two Double Bonds, $C_nH_{2n-4}O_2$; Linolic Acid, $C_{18}H_{32}O_2$. — In many plant oils there occur fatty acids which tend to take up oxygen and harden to a resin-like state. Such acids show a chemical behavior which indicates that they possess two double bonds. These are [illegible] acid because of their prevalence in linseed [illegible] this class of acids are found espe- [illegible] walnut, cedar, and hemp oils and to [illegible] oil and in many other oils, but not in [illegible] of the whole as in linseed oil. On this [illegible] the peculiar value of the latter oil for [illegible] of paints.

[illegible] acid still remains an oil at −18°. It absorbs 4 [illegible] or two molecules of hydriodic acid. On [illegible] a tetrahydroxy derivative. On vigor- [illegible] with hydriodic acid and phosphorus, it [illegible] acid. Like oleic and stearic acids, linolic [illegible] normal and not a branched structure. The [illegible] linolic acid is soluble in all the ordinary fat [illegible] petroleum ether. This last solvent dis- [illegible] from stearic acid, and can be employed [illegible] means of distinguishing between the two.

[illegible] Double Bonds, $C_nH_{2n-6}O_2$; **Linoleic** [illegible] This acid occurs especially in linseed [illegible] higher degree the "drying" property. [illegible], and when oxidized with dilute [illegible] a hexahydroxy stearic acid. The [illegible] contain fatty acids containing two [illegible]

[illegible] that the solubility of the hy- [illegible] water rapidly increases with increas- [illegible] groups. Dihydroxy stearic acid [illegible] stearic acid, difficultly [illegible] of the hexahydroxy acid is [illegible]

CHAPTER VIII

THE FATS, WAXES, AND RELATED COMPOUNDS

89. The Animal Fats. — Most important among the animal fats are the body fats of the ox, sheep, and swine, and butter fat. As has already been stated, fats are the glycerol esters of the higher fatty acids. The body fats of animals react practically neutral, and contain but a trace of volatile fatty acids. The relative amounts of the different acids contained in the fats of different species differs widely and even the fats from the same species vary in composition with the character of the food fats. Thus *lard*, which is the collective term for the fat of the hog, may melt as low as 28° when the diet consists of corn meal only, when it contains over 90 per cent of olein; or as high as 35.6° when the animals are fed a ration of oats, peas, and barley.

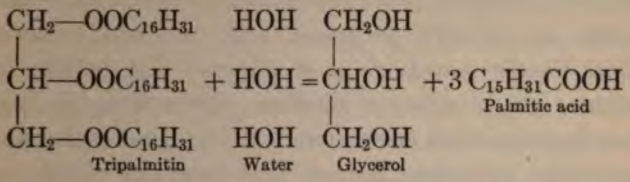
From the same animal the body fats from different parts may show different melting points owing to their variable content of olein. Thus the fats surrounding the kidney may melt as high as 43° in the hog. Triolein is a liquid at 0°, while tripalmatin and tristearin melt at 62 and 71.5° respectively. Human fat is especially rich in olein, frequently melting as low as 17.5°, while tallow regularly melts at 45–46° and the fat of the sheep at 46–51°. The sp. gr. .960–.968. Other fats range in specific gravity from .850 to .950.

91. Properties of the Fats. — Since the natural fats do not represent individual chemical compounds, but mixtures of several kinds, their physical properties depend upon the proportions in which they are mixed, and especially on the content of olein. They are insoluble in water, but slightly soluble in cold alcohol. They are readily soluble in ether, petroleum ether, benzene, chloroform, and in other solvents.

The fats can be heated to 200–250° without undergoing any essential change, but above this temperature they evolve the irritating vapors of acrolein ($CH_2 = CH—CHO$), which causes profuse secretion of tears. This has its origin from glycerol, from which it is formed by the loss of two molecules of water (**85**). This test is best carried out by heating the fat with potassium bisulphate ($KHSO_4$). This acrolein test serves to distinguish the fats from the mineral oils, oily esters, and other substances having the physical properties of fats or oils.

The commercial fats on keeping become rancid. This is due to the action of the oxygen of the air, especially in the presence of light, which greatly accelerates their oxidation. In the process of becoming rancid the neutral fats become acid in reaction. Fats, especially from plant sources, are liable to become acid in reaction owing to their containing the enzyme *lipase,* which accelerates the hydrolysis of esters into alcohol and acid. In part the rancidity of impure fats is brought about by the action of bacteria on the proteins, carbohydrates, etc., with which they are contaminated.

The fats are all saponifiable (hydrolyzable), as are other esters:



$$\begin{array}{l} CH_2-OOC_{16}H_{31} \\ | \\ CH-OOC_{16}H_{31} \\ | \\ CH_2-OOC_{16}H_{31} \\ \text{Tripalmitin} \end{array} \quad \begin{array}{c} HOH \\ \\ +\,HOH \\ \\ HOH \\ \text{Water} \end{array} = \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \\ \text{Glycerol} \end{array} + 3\,\underset{\text{Palmitic acid}}{C_{15}H_{31}COOH}$$

Hydrolysis can be effected by heating with water alone under pressure, but takes place slowly because of the great insolubility of fats in water. Both acids and alkalies greatly accelerate the reaction. Technically enormous quantities of fats are saponified by means of sodium hydroxide for the preparation of soap, and for the production of glycerol (glycerine). In the laboratory fats are usually saponified with an alcoholic solution of potassium hydroxide, in which the fats are much more soluble than in water. Their solution greatly facilitates the reaction.

92. Soaps. — Soap is made by boiling the fats with a solution of sodium hydroxide until saponification is complete. Sodium soaps are readily soluble in water, but not in strong brine, so common salt is added to precipitate the soaps. The solution from which the soap separates contains the excess of lye (NaOH) together with the glycerol formed in saponification. From the evaporated residue of this solution glycerol is prepared by distillation under diminished pressure. The soap, which has been precipitated in a flaky form, is separated, melted, and cast in molds.

ions. The acid ions combine with the hydrogen ions of the water to form undissociated fatty acid molecules. The acids thus liberated combine with a molecule of soap and form insoluble substances which give the milky appearance to water solutions of soap. The amount of free alkali produced depends on the degree of dilution of the soap solutions. Strong soap solution scarcely causes the pink color characterisitc of alkalies with phenolphthalein, and the depth of pink steadily increases as the solution is diluted with water.

When fats come into contact with soap solutions, they tend when agitated to form an emulsion, *i.e.* the droplets of fat break up into very fine particles, each surrounded by a film of soap solution which separates each drop from its fellows and prevents their union into larger drops and consequent separation. The action of soap in removing grease is therefore twofold: the free alkali will saponify a part of the fats and thus part will pass into solution as soap; the remainder is emulsified and remains permanently suspended in the soap solution.

As the free alkali is used up by the saponification of fats, more soap dissociates to replace that which has disappeared. Soap therefore serves as a reserve supply of alkali, and in washing there is automatically maintained a constant content of hydroxyl ions in solution without at any time an undesirably high content. Soap is for this reason superior to a free alkali solution for washing. A dilute solution of the latter would show a progressive decrease in hydroxyl ions as its use progressed.

Soap does not readily remove the higher hydrocarbons, such as vaseline, unless there is simultaneously present some fat or oil.

94. Methods for the Characterization of the Fats. — The chemical nature of the fats is indicated by their physical characters and by their behavior toward certain chemical reagents.

The *melting point* and the temperatures at which the fats solidify after having been melted serve to show the general nature of the fats, whether principally stearin or palmatin, or containing much olein.

The *acid number* gives the milligrams of KOH necessary to neutralize the free fatty acids contained in one gram of fat. For its determination, 1–2 grams of the fat in 12–15 c.c. of a mixture of 1 part of alcohol and 2 part of ether, which should react neutral to phenolphthalein indicator, are titrated, using this indicator with a 1/10 normal solution of potassium hydroxide in alcohol. Fresh animal fats are nearly neutral, but on becoming rancid or on long keeping the acidity rises markedly. This number gives an idea as to the state of freshness of the fats.

Saponification Number. — Since each molecule of fat reacts with three molecules of potassium hydroxide to form glycerol and three molecules of soap, the number of carbon atoms in the fatty acids contained in the fats will determine whether little or much alkali will be necessary to saponify a standard quantity of fat. The saponification number indicates the number of milligrams of potassium hydroxide necessary to neutralize the fatty acids derived from one gram of fat. It is determined by dissolving a weighed amount of fat in a carefully standardized solution of potassium hydroxide in alcohol, and heating until saponification is complete. Water is then added and the free alkali in the solution is titrated by the addition of standard acid to the neutral point, using phenolphthalein as indicator. The difference between the KOH content of the solution employed to saponify the fat and the alkali remaining unneutralized after the saponification shows how much alkali has been neutralized by the fatty acids formed. Essentially this method is a determination of the molecular weight of the fat, as the following table shows:

	Mol. Weight	Saponification No.
Butyrin	302	557.3
Caproin	336	436.1
Palmatin	806	208.8
Stearin	890	189.1
Olein	884	190.4

Unsaponifiable Residue. — It is obvious that the saponification number can give reliable data concerning the molecular weights of the fatty acids contained in the fats, only when glycerol is the only alcohol present in the fats. Now it not infrequently happens that there occur with the fats certain other alcohols, as cetyl and octadecyl alcohols and cholesterol ($C_{27}H_{43}OH$), an alcohol of high molecular weight which is structurally very different from the higher alcohols derived from the aliphatic hydrocarbons (**99**). These occur free or in ester linkage with fatty acids. Cholesterol possesses physical properties very similar to the fats and fatty acids, and occurs free and as esters almost universally distributed in animal and plant tissues. Since these alcohols have molecular weights of 242, 270 and 384 respectively, whereas that of glycerol is but 92, the saponification number can be properly interpreted only when the content of these higher alcohols is known.

These alcohols are collectively estimated by repeatedly shaking with petroleum ether the solution of the soaps, glycerol, and higher alcohols obtained in the determination of the saponification number after again making it alkaline after the titration. Petroleum ether does not dissolve soaps, glycerol, or potassium hydroxide, but readily dissolves the higher alcohols in question. After separating the petroleum ether, filtering, and evaporating it, and again taking up the residue of higher alcohols in a fat solvent such as ether, the solution is filtered, and the solvent evaporated in a weighed dish. The residue is weighed after keeping the dish in a desiccator until its weight is constant. This weight represents the higher alcohols which were present in the sample of fat.

A few typical values of the higher alcohols in some common fats will illustrate the importance of this determination.

	UNSAPONIFIABLE MATTER
Linseed oil	.42–1.0
Olive oil	.46–1.0
Castor oil	.30–.40
Corn oil	1.35–2.90
Wheat oil	4.45
Human fat	.33
Lard	.30–.40

Shark liver oil	7.0–10.5
Sperm oil	37.0–41.0
Beeswax	52.0–56.0

The Iodine Number. — The relative content of saturated and unsaturated fatty acids in fats is determined by the capacity of the fats to absorb iodine. As an example of the determination of this value, the Hübl method will be described:

(1) A standard solution of iodine containing 25 grams of iodine and 30 grams of mercuric chloride dissolved in 500 c.c. of alcohol, free from fusel oil.

(2) A solution of sodium thiosulphate containing 24 grams of the salt per liter. This solution is standardized by determining the number of milligrams of iodine which is reduced by a cubic centimeter of the solution.

The sample of fat, .3 to .4 gram of olein-rich fats or .8 to 1 gram of solid fats, is weighed into a glass stoppered bottle and dissolved in 15–25 c.c. of chloroform. It is then heated with 25 c.c. of the iodine solution. After 6 to 10 hours 20 c.c. of a 10% potassium iodide solution is added, the whole diluted with water, and the unabsorbed iodine is titrated by means of the sodium thiosulphate solution. The KI is added to prevent the separation of iodine in the solid state on dilution with water.

The following values illustrate the iodine values for several kinds of fats:

	IODINE NUMBERS PURE FATS
Olein	86.2
Linolein	173.6
Linolenin	262.2

IODINE NUMBERS OF NATURAL FATS

Linseed oil	170–200
Hempseed oil	145–150
Almond oil	93–97
Olive oil	80–88
Palm oil	51
Coconut oil	8–9
Tallow (beef)	38–45
Tallow (mutton)	35–45
Lard	50–70
Butter	26–38

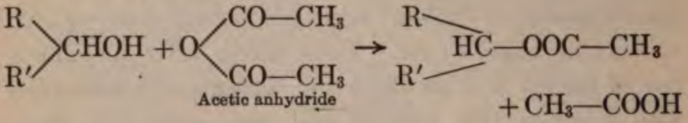
Reichert-Meissl Number (*Volatile fatty acid number*).— It has already been stated that certain fats contain much larger amounts of the fatty acids of lower molecular weight, as butyrin, caproin, etc. These acids, after saponification of the fat with an alkali and subsequent acidification with a non-volatile mineral acid, pass over with steam when the mixture of fatty acids and water is distilled. The distillate is titrated with standard alkali, using phenolphthalein as indicator. *The number of cubic centimeters of* 1/10 *normal alkali required to neutralize the volatile acids from* 5 *grams of fat constitute the Reichert-Meissl number.*

The values of the Reichert-Meissl number for some of the more important fats are as follows:

Linseed oil	0.0	Palm oil	5.0–7.0
Olive oil	0.6	Coconut oil	6.5–7.0
Lard	.7	Croton oil	12.–13.5
Tallow	.5	Butter fat	21–33.0
Goose fat	.2– 2		

This method of examination is of great service for the examination of butter for adulteration. No other fat approximates the high value of butter fat in volatile fatty acids, and the lowering of this value by the addition of vegetable fats or the body fats of animals is readily detected.

Acetyl Number.—Very few of the natural fats contain hydroxylated fatty acids. Chief among these is castor oil, which in ricinoleic acid contains a secondary alcohol group (**90**). The amount of hydroxy fatty acids is arrived at through treatment of the fat with acetic anhydride (**64**) and heat, whereby the hydroxyl group of the fat forms an acetic ester:



$$\begin{matrix}R\\ R'\end{matrix}\!\!>\!CHOH + O\!<\!\begin{matrix}CO{-}CH_3\\ CO{-}CH_3\end{matrix} \rightarrow \begin{matrix}R\\ R'\end{matrix}\!\!>\!HC{-}OOC{-}CH_3 + CH_3{-}COOH$$

Such esters are stable to boiling water, and the excess of acetic anhydride can be converted into acetic acid by boiling:

$$(CH_3{-}COO)_2O + H_2O = 2CH_3{-}COOH$$

The acetylated fats are then separated mechanically, since they are insoluble in water and form a layer. After washing these free from acid reaction and collecting on a filter paper they are dried at 100° to constant weight. A carefully weighed sample (2–5 grams) is then saponified with an excess of carefully measured standard solution of alcoholic potassium hydroxide N/10. When saponification is complete, the same volume of N/10 acid is added as was added of N/10 alkali in the saponification and the solution warmed. The aqueous layer is then siphoned off through filter paper and the remaining oil is washed until all soluble acids are washed out. The filtrate and washings are titrated with N/10 alkali, using phenolphthalein as an indicator. Soluble fatty acids must be determined separately and their amount deducted from the value found.

The following table shows the values for the acetyl number of some common fats:

Linseed oil	4.0	Beeswax	15.2
Olive oil	10.5	Cod liver oil	4.8
Palm oil	18.0	Shark liver oil	12.0
Lard	2.6	Seal fat	16.5
Tallow (beef)	2.5–8.6	Spermaceti	4.5
Wool wax	23.0		

The *elaidin test* depends upon the fact that oleic acid changes from the *cis* to the *trans* form (**86**) with a marked rise in melting point when treated with nitrous oxide. The test is carried out by placing the oil (10 c.c.) in a test tube with nitric acid (.5 c.c.) underneath it, and placing in the acid a piece of copper (.2 gm.). If much oleic acid is present, the fat will have become solid at the temperature of 25° by the following day. Fats having two or three double bonds do not give this test.

The Hexabromide Test.—Dibrom and tetrabrom stearic acids result from the absorption of bromine by oleic and linolic acids or their fats. Both of these are soluble in ether. Linolenic acid having three double bonds, yields a produced by a leaf louse in Finland, is the ester formed of psylla alcohol, $C_{33}H_{67}OH$, and psylla acid, $C_{33}H_{66}O_2$. *Beeswax* consists principally of myricyl alcohol and cerotic and melissic acids in ester combination. It is employed by the honeybees for protecting their eggs and larvæ against cold and also for honeycomb. It also contains impurities gathered from plants.

The gland at the base of the tail in birds secretes a liquid wax which the birds spread over their feathers to render them waterproof and soft. This wax consists of palmitic, stearic, and oleic acid esters of octadecyl alcohol, $C_{18}H_{38}O$.

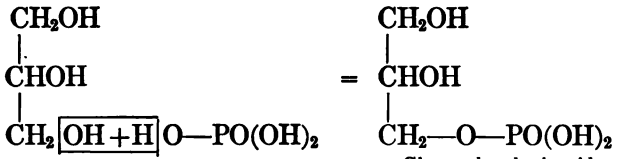
Spermaceti is a wax, principally cetyl palmitate, which is obtained from a cavity in the head of the sperm whale. From this cavity a canal runs to the tail and branches communicate with pockets in the panniculus. The wax is thus conveyed to all parts of the skin, which it permeates and protects from the action of the sea water. Similar esters are found in whale oil and in the oil from dolphins.

The production of spermaceti is closely analogous to the secretion of wax by the tail glands of birds and to the universal distribution of the sebaceous glands in the skin of the higher animals which produce an oily secretion of liquid wax which protects the skin and hair.

Wool wax (lanolin), the natural covering of sheep's wool, contains much cholesterol and oxycholesterol in the free state, and also as esters of several fatty acids, especially myristic, cerotic, and lanoceric. Wool wax also contains other higher alcohols, as carnaubyl, $C_{24}H_{50}O$, and lanolin alcohol, $C_{12}H_{24}O$.

96. Lecithins and other Phosphatides. — As constituents of every living cell, both animal and plant, there occur compounds closely related to the fats, called *lecithins.* These on hydrolysis yield one molecule of glycerol, two of fatty acid, one of orthophosphoric acid (H_3PO_4), and one of choline (**48**).

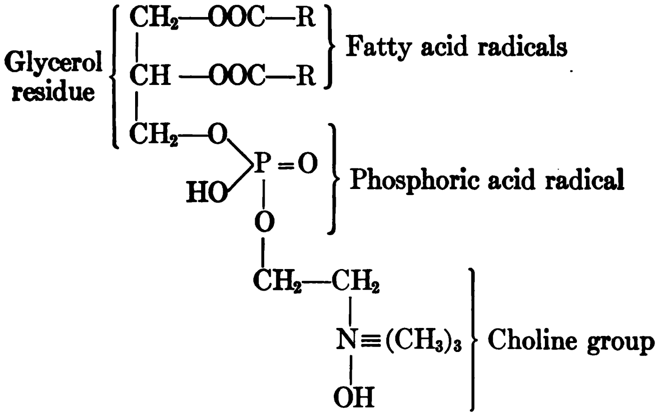
Glycerol forms with phosphoric acid an ester, *glycerophosphoric* acid:



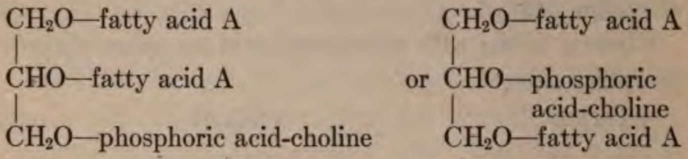
$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2\boxed{OH+H}O—PO(OH)_2 \end{array} = \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2—O—PO(OH)_2 \end{array}$$

Glycerophosphoric acid

Lecithins are regarded as complexes of the following structure:



Little is known with certainty of the chemistry of the various lecithins. It is evident that different fatty acids in the molecule would lead to lecithins of different properties. Furthermore there is the possibility that two different fatty acids may be linked in the same molecule, forming mixed lecithins. Isomerism is likewise possible due to the different linking of the phosphoric acid-choline group:



$$\begin{array}{l} CH_2O\text{—fatty acid A} \\ | \\ CHO\text{—fatty acid A} \\ | \\ CH_2O\text{—phosphoric acid-choline} \end{array} \quad \text{or} \quad \begin{array}{l} CH_2O\text{—fatty acid A} \\ | \\ CHO\text{—phosphoric acid-choline} \\ | \\ CH_2O\text{—fatty acid A} \end{array}$$

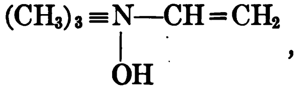
The investigation of this class of compounds presents almost insurmountable difficulties. They are of a waxy nature, and do not form compounds with other substances which can be crystallized, for purposes of purification, and they cannot be distilled without decomposition, and have no definite melting point. There is therefore no criterion by which to judge when one is in possession of an individual chemical compound or is dealing with a mixture, except constancy of composition of the material after repeated solution and precipitation of the lecithin. This is carried out in most instances by dissolving the lecithin in ether and pouring the solution into a large volume of acetone in which lecithin is insoluble. The precipitates are always amorphous. When on repeating this method of purification the precipitate is found to contain the same percentages of nitrogen and phosphorus, these being the easiest elements to determine quantitatively, the assumption is often made that the precipitated material represents a chemical individual. Instances are known however in which two substances precipitate in fairly constant proportions under such conditions, so that such a method of purification cannot inspire much confidence.

Among the compounds formed by lecithin which have a crystalline structure, and which are serviceable for its purification, are the cadmium chloride double salt, which can be crystallized from a mixture of benzene and alcohol.

The lack of satisfactory criteria of purity for compounds of this class has rendered their investigation uninviting as compared with other lines of study. This in a measure accounts for the paucity of our knowledge of these compounds.

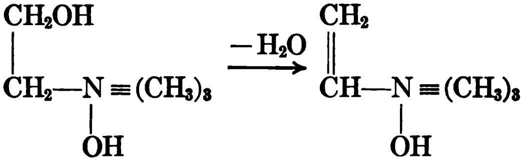
Birds when fed certain fat-free and lecithin-free foods can grow and produce eggs containing much larger amounts of lecithins than the bodies of the birds contained at the beginning of the experiment. The lecithin complex is therefore synthesized in the animal cells from its constituents. It has been pointed out (**92**) that fatty acids and glycerol can be formed by the animal body from sugars and proteins. The synthesis of lecithin by birds shows that the choline complex is also synthesized by the animal cells. Diets on which birds accomplished this synthesis contained neither glycol nor trimethylamine. The steps by which choline is formed are not clearly understood, but it is evident that the animal cells can, under certain conditions, form methylated nitrogen compounds, as trimethylamine, as it is known to do with tellurium and selenium (**6**).

Neurine,



$$(CH_3)_3\equiv\underset{\substack{|\\ OH}}{N}-CH=CH_2$$

, *trimethyl-vinyl-ammonium hydroxide.*—We are by no means certain that choline is the only nitrogen base contained in the natural compounds of the lecithin type. Thudicum, a worker of distinction in this field, states that from certain phosphatides of the brain (cephalin) he obtained *neurine*. It is highly probable that bases other than choline exist in lecithins. Neurine is derived from choline by the loss of a molecule of water:

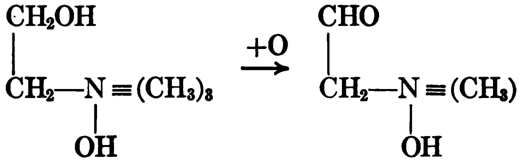


$$\begin{array}{l} CH_2OH \\ | \\ CH_2{-}N{\equiv}(CH_3)_3 \\ \quad\;\, | \\ \quad\;\, OH \end{array} \xrightarrow{-H_2O} \begin{array}{l} CH_2 \\ \| \\ CH{-}N{\equiv}(CH_3)_3 \\ \quad\;\, | \\ \quad\;\, OH \end{array}$$

Choline Neurine

Neurine is much more toxic than choline.

Choline, being an alcohol as well as a base, can yield an aldehyde on oxidation:



$$\begin{array}{l} CH_2OH \\ | \\ CH_2{-}N{\equiv}(CH_3)_3 \\ \quad\;\, | \\ \quad\;\, OH \end{array} \xrightarrow{+O} \begin{array}{l} CHO \\ | \\ CH_2{-}N{\equiv}(CH_3) \\ \quad\;\, | \\ \quad\;\, OH \end{array}$$

Muscarine

As an alcohol, choline yields esters with various acids. These in general possess pronounced pharmacological properties, being much more toxic than choline itself.

97. Muscarine, a highly toxic substance, occurs in some of the poisonous mushrooms, but appears not to be toxic enough to account for all of their poisonous properties.

Other phosphatides (compounds yielding fatty acids, glycerol, some nitrogen-containing base, and phosphoric acid) have been described, among them cephalin, the acids of which are more unsaturated than those of ordinary lecithins. The base is apparently not choline. It is not as yet satisfactorily studied.

98. The Cerebrosides. — There is found in the nervous tissue a group of substances which contain no phosphorus, but yield on hydrolysis a nitrogen-containing base of unknown chemical nature, a sugar (galactose), and a fatty acid. They are not found in embryonic nervous tissues, but develop during medullation. Two such compounds are *phrenosin* and *kerasin*. They still need further study to reveal their chemical structure.

99. Sterols. — The brain at different ages contains varying amounts of *cholesterol* (4–9 %) and possibly several more or less closely related compounds of this nature. Its content increases with age. As stated under waxes (**95**) cholesterol is an alcohol of high molecular weight. Its formula is represented by $C_{27}H_{46}O$. Several of its esters are known. Its structure has been in part elucidated. Its alcohol group is a secondary one, since it oxidizes to a ketone. It also contains a double bond, as shown by its forming an addition product with bromine or iodine. The structure of the rest of the molecule is not yet established. Compounds closely related to cholesterol are found in the fats of plants. These are called *phytosterols*.

Cholesterol is a crystalline solid, insoluble in water, sparingly soluble in cold, but readily in hot, alcohol, ether, acetone, chloroform, and other organic solvents. Cholesterol melts at 147 °. It forms an acetyl derivative (ester) when heated with acetic anhydride, which melts at 114° and is useful in identifying cholesterol.

Cholesterol forms with a natural glycoside, digitonin, a compound sparingly soluble in 95 % alcohol. It is frequently precipitated in this form and weighed in its quantitative estimation.

An *isocholesterol* has been described as occurring in lanolin, and a derivative called *coprosterol* has been isolated from feces. It has no double bond and results from the reduction of cholesterol, due to bacterial action.

CHAPTER IX

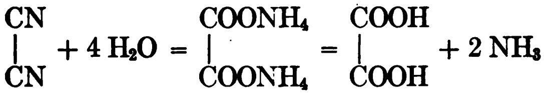
THE DIBASIC ACIDS

100. It has been shown how hydrocyanic acid reacts with water, forming ammonium formate (**50**). In fact, solutions of HCN are unstable, tending to react with water:

$$HCN + 2\,H_2O = HCOONH_4$$

Hydrocyanic acid is therefore the nitrile of formic acid.

Cyanogen, $\begin{array}{c}CN\\ |\\ CN\end{array}$, on the other hand, when heated with acids reacts with water to form oxalic acid:



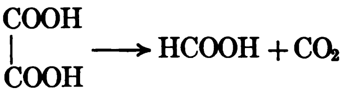
$$\begin{array}{l}CN\\ |\\ CN\end{array} + 4\,H_2O = \begin{array}{l}COONH_4\\ |\\ COONH_4\end{array} = \begin{array}{l}COOH\\ |\\ COOH\end{array} + 2\,NH_3$$

Ammonium oxalate

Cyanogen has therefore the double formula indicated. Oxalic acid occurs in nature in many plants — rhubarb, sorrel, etc. It is deposited as its salt, calcium oxalate, in the leaves and cells. These crystals have the appearance of envelopes. Oxalic acid is of great importance in analytical chemistry. By reason of its possession of two carboxyl groups it forms two series of salts, acid and neutral. The most important salts are the acid potassium and the neutral calcium salt. The former is present in the juices of many plants, from which it is obtained in a crystalline form on evaporation. The calcium salt is so slightly soluble in water and in dilute acetic acid that it is employed for the quantitative estimation of calcium.

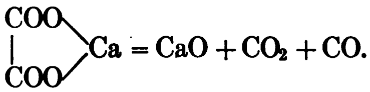
The salt of urea with oxalic acid is soluble in 23 parts of water and in 60 parts of alcohol. This compound has been employed for the isolation of urea from urine.

With great care and with proper conditions oxalic acid can be decomposed by heat into formic acid and carbon dioxide:



$$\begin{array}{l}COOH\\ |\\ COOH\end{array} \longrightarrow HCOOH + CO_2$$

On heating strongly the formic acid decomposes into water and carbon monoxide. The calcium salt on being heated forms calcium carbonate (calcium oxide + carbon dioxide) and carbon monoxide:

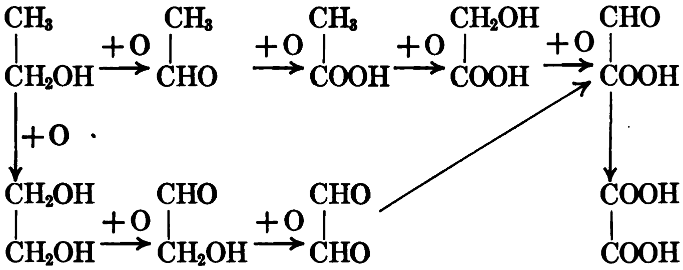


$$\begin{array}{l}COO\\ |\\ COO\end{array}\!\!>Ca = CaO + CO_2 + CO.$$

Oxalic acid can also be formed by quickly raising sodium formate to a high temperature.

$$2\,HCOONa = H_2 + (COONa)_2$$

Dehydrating agents such as concentrated sulphuric acid decompose oxalic acid, forming carbon monoxide, carbon dioxide, and water. This is a convenient way of preparing carbon monoxide. Characteristic of oxalic acid is its conversion into volatile products without charring when heated on platinum, and also the absence of charring when it is heated with concentrated sulphuric acid. In dilute sulphuric acid it is easily oxidized by potassium permanganate solution. This decolorization of dilute permanganate solutions is caused by many other compounds. It is also formed by the oxidation of many organic substances such as starch, wood, etc. It results from the oxidation of alcohol by potassium permanganate. The various stages through which the oxidation may pass are illustrated by the following scheme:



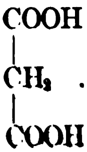
This series of compounds illustrates what not infrequently happens in reactions involving the oxidation of organic compounds. The reaction does not proceed with the formation of the end products indicated by the simple equations usually written, but stepwise, and with the formation of a number of oxidation products. Only because the oxalic acid is highly resistant to further oxidation under certain conditions does the reaction stop at this point instead of going on to carbon dioxide and water. In many synthetic reactions the same type of change occurs, viz. there is a principal reaction accompanied by a number of side reactions which form by-products and diminish the yield of the desired substance. By allowing the reaction to proceed for but a short time or conducting it at low temperatures, etc., the intermediary compounds can frequently be accumulated in greater amounts.

Properties of Oxalic Acid. — It crystallizes from water in colorless prisms containing two molecules of water of crystallization. In this form it melts at 101.5°. On being heated for a time at 100° it loses its water and forms a white powder of *anhydrous* acid which melts at 189°. It dissolves readily in alcohol but very slightly in ether, and is insoluble in chloroform, petroleum ether, and benzene.

Oxalic acid is a strong acid. On evaporating a solution of sodium chloride with oxalic acid, sodium oxalate crystallizes out, and on heating a mixture of sodium chloride and oxalic acid, hydrochloric acid gas is evolved. It is a corrosive poison which acts very quickly. In general it cannot serve as a source of carbon for molds or bacteria, but there are some observations tending to show that certain organisms can so use it. Oxalic acid is produced from sugars by certain molds.

In the higher animals oxalic acid is burned to but very slight extent.

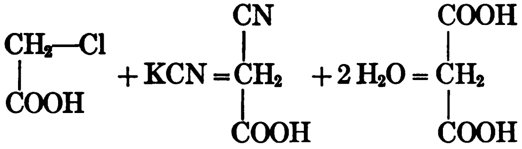
The dibasic acids form esters, amides, etc., as do the monobasic acids. There is in each case, however, a derivative possible in which but one carboxyl is substituted, as well as one derived by the reaction of both acid radicles.

101. Malonic Acid, 

$$\begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

.—This acid results from the

nitrile which is formed by the reaction of monochloracetic acid with potassium cyanide:



$$\begin{array}{l}CH_2\text{—}Cl\\|\\COOH\end{array} + KCN = \begin{array}{l}CN\\|\\CH_2\\|\\COOH\end{array} + 2\,H_2O = \begin{array}{l}COOH\\|\\CH_2\\|\\COOH\end{array}$$

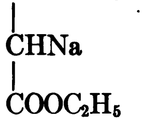
This method of synthesis makes clear its structure.

Malonic acid is a crystalline compound melting at 132°. It is found in beet juice. On heating to 140–150° it decomposes with the formation of carbon dioxide and acetic acid:

$$COOH\text{—}CH_2\text{—}COOH = CO_2 + CH_3\text{—}COOH$$

This property is common to the dibasic acids in which the two carboxyl groups are linked to one carbon atom. When heated above their melting points they lose one molecule of carbon dioxide.

102. Malonic Ester Synthesis. — The most important derivative of malonic acid is its diethyl ester. It is a liquid with a slight odor which boils at 195°. It is remarkable for the peculiar behavior of the hydrogen atoms of its methylene group. When malonic ester is treated with sodium, hydrogen is evolved and a metallic derivative, ***sodiomalonic ester,*** is formed:

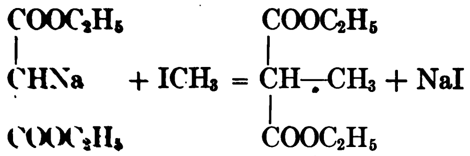


$$\begin{array}{l}COOC_2H_5\\|\\CHNa\\|\\COOC_2H_5\end{array}$$

Sodiomalonic ester

This property of the hydrogen atoms of methylene groups being replaceable by metals is found only in compounds in which the methylene group is linked on both sides to strongly negative groups. Other instances of this character will appear later (see aceto-acetic acid, **127**).

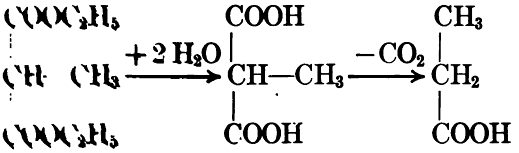
This compound reacts with alkyl iodide just as do the sodium alcoholates (**24**), the sodium being replaced by the alkyl groups:



$$\begin{array}{l} COOC_2H_5 \\ | \\ CHNa \\ \\ COOC_2H_5 \end{array} + ICH_3 = \begin{array}{l} COOC_2H_5 \\ | \\ CH-CH_3 \\ | \\ COOC_2H_5 \end{array} + NaI$$

Malonic ester

The resulting alkyl derivative on saponification yields *methylmalonic acid*, which on heating above its melting point decomposes into *propionic acid*.

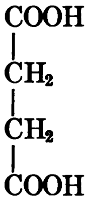


$$\begin{array}{l} COOC_2H_5 \\ | \\ CH-CH_3 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{+2H_2O} \begin{array}{l} COOH \\ | \\ CH-CH_3 \\ | \\ COOH \end{array} \xrightarrow{-CO_2} \begin{array}{l} CH_3 \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

By treating methylmalonic ester with sodium the second hydrogen is replaced by metal and this in turn can be substituted by methyl, ethyl, etc. groups, which on loss of CO_2 yield *dimethyl*, methyl-ethyl, etc., derivatives of acetic acid, viz. *isobutyric* and *isovaleric* acids. The [illegible] [illegible] synthesis is therefore a general method for [illegible] [illegible] of the isomeric *monobasic fatty acids* as well [illegible] [illegible] of homologues of malonic acid.

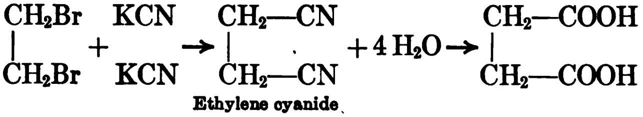
Malonic acid and urea condense to barbituric acid (**139**).

103. Succinic Acid. —



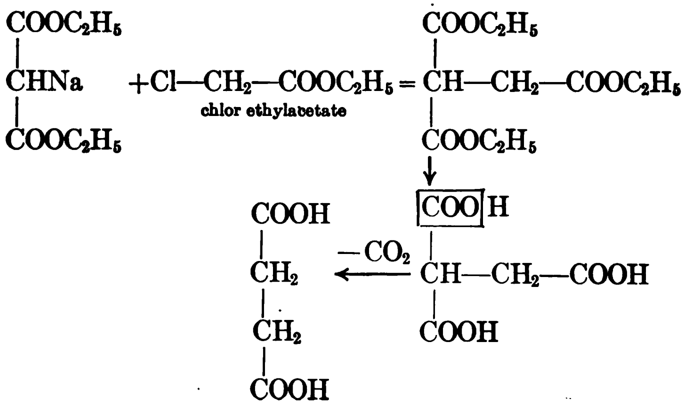
$$\begin{matrix}COOH\\|\\CH_2\\|\\CH_2\\|\\COOH\end{matrix}$$

This acid occurs in the urine after ingestion of asparagus. It is found in amber, fossilized wood, and many plants. It is crystalline and melts at 182°. That this acid is a homologue of malonic acid is shown by its synthesis from ethylene bromide, through ethylene cyanide, which on hydrolysis yields succinic acid.



$$\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} + \begin{matrix}KCN\\ \\KCN\end{matrix} \rightarrow \underset{\text{Ethylene cyanide}}{\begin{matrix}CH_2—CN\\|\\CH_2—CN\end{matrix}} + 4\,H_2O \rightarrow \begin{matrix}CH_2—COOH\\|\\CH_2—COOH\end{matrix}$$

The dibasic acids can likewise be synthesized by the malonic ester synthesis. Not only does sodiomalonic ester react with alkyl halides (**102**), but with halogen derivatives such as the ester of chloracetic acid:



$$\begin{matrix}COOC_2H_5\\|\\CHNa\\|\\COOC_2H_5\end{matrix} + \underset{\text{chlor ethylacetate}}{Cl—CH_2—COOC_2H_5} = \begin{matrix}COOC_2H_5\\|\\CH—CH_2—COOC_2H_5\\|\\COOC_2H_5\end{matrix}$$

$$\downarrow$$

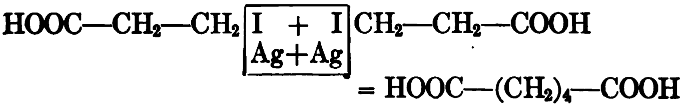
$$\begin{matrix}COOH\\|\\CH_2\\|\\CH_2\\|\\COOH\end{matrix} \xleftarrow{-CO_2} \begin{matrix}\boxed{COO}H\\|\\CH—CH_2—COOH\\|\\COOH\end{matrix}$$

boil at 304°. It is easily soluble in water, alcohol and ether.

106. Glutamic Acid, $COOH—CH_2—CH_2—CHNH_2—COOH$, *a-amino glutaric acid,* is present in many proteins, forming about 40 % of the total nitrogen content of the wheat proteins, gliadin and glutenin. The naturally occurring form is dextrorotatory, but its salts rotate the plane of polarized light to the left. Its diethyl ester boils under 10 mm. pressure at 139–140°. Glutamic acid is soluble at 16° in 100 parts of water. It forms salts with both acids and bases as does aspartic acid (**104**). Of special importance for its isolation is the hydrochloride, which is very sparingly soluble in concentrated hydrochloric acid. On saturating its solutions with hydrochloric acid gas the hydrochloric acid salt separates on cooling nearly quantitatively. This property differentiates it from aspartic acid (**120**).

107. Glutamine, $CONH_2—CH_2—CH_2—CHNH_2—COOH$, is found widely distributed in the sap of plants. After everything which is precipitable by lead has been removed from plant extracts, glutamine is precipitated by mercuric nitrate. Certain other amino acids are likewise precipitated with it, so that its purification is not simple. It is much more soluble in water than is asparagine. It seems highly probable that glutamic acid occurs within the protein molecule as glutamine. On hydrolysis with acids the amide group is converted into ammonia (**90**).

108. Adipic Acid, $COOH—(CH_2)_4—COOH$, is said to occur in beet juice. It is formed by the action of silver on β-iodio propionic acid.



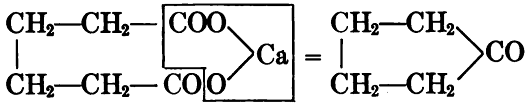
$$\mathrm{HOOC{-}CH_2{-}CH_2}\boxed{\begin{array}{c}\mathrm{I + I}\\ \mathrm{Ag{+}Ag}\end{array}}\mathrm{CH_2{-}CH_2{-}COOH} = \mathrm{HOOC{-}(CH_2)_4{-}COOH}$$

It melts at 148°. It is of interest mainly because it is convertible into a ring structure. This will be described later (**111**).

Pimelic Acid, $COOH—(CH_2)_5—COOH$, has not been found in nature. It melts at 103°, and is soluble in 25 parts of water at 20°.

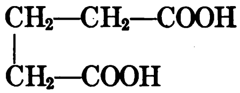
Suberic Acid, $COOH—(CH_2)_6—COOH$, melts at 141°. At 15.5° one part of the acid is soluble in 600 parts of water.

tions which are of interest, starting with the calcium salt of adipic acid:



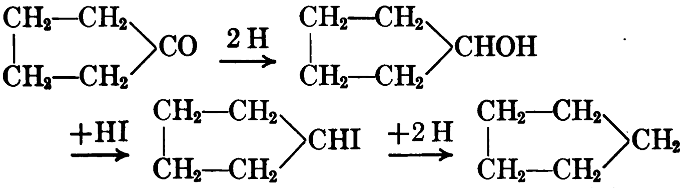
Calcium adipate Ketopentamethylene

The structure of the ketone derivative of pentamethylene is further shown by the fact that it oxidizes to glutaric acid:



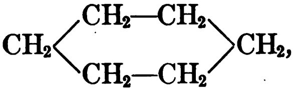
$$\begin{array}{l} CH_2—CH_2—COOH \\ | \\ CH_2—COOH \end{array}$$

Pentamethylene itself is obtained by reducing its ketone derivative to a secondary alcohol, then replacing the hydroxyl of the alcohol by iodine by treatment with hydriodic acid, followed by the replacement of the iodine by hydrogen:



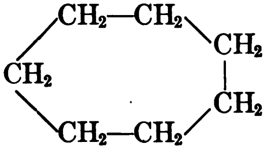
Pentamethylene

Pentamethylene is a liquid boiling at 50°. It will be recalled that normal pentane boils at 37°. While the tetramethylene ring shows a tendency to open and add two halogen atoms, it does not undergo this change as readily as does trimethylene. Pentamethylene, however, is so stable that it does not react with bromine. It is exceedingly stable toward oxidizing agents, as nitric acid, and shows none of the tendency of unsaturated compounds to condense with sulphuric acid (**125**).

112. Hexamethylene,  is formed from the calcium salt of normal pimelic acid in a manner entirely analogous to that described for the formation of pentamethylene.

Hexamethylene is stable toward oxidizing agents such as potassium permanganate, and does not form an addition product with bromine. It has an odor like petroleum, and boils at 69°.

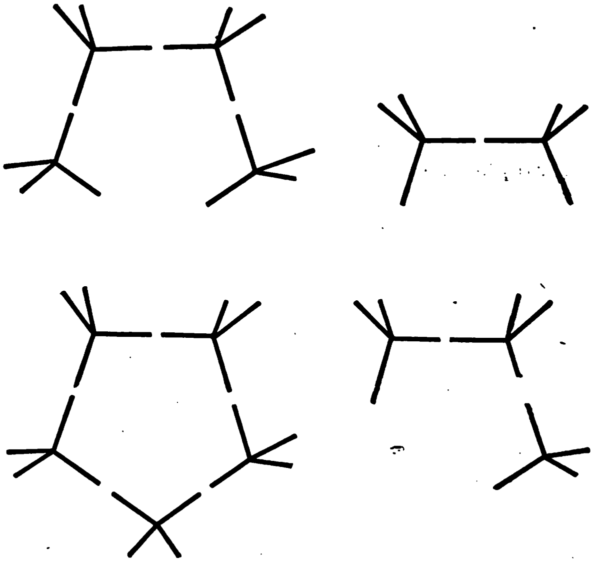
113. Heptamethylene,



The ketone derivative of this hydrocarbon can likewise be prepared in the manner just described by dry distillation of the calcium salt of suberic acid, $COOH—(CH_2)_6—COOH$. And an eight-membered ring results from the calcium salt of azeliac acid, $COOH—(CH_2)_7—COOH$.

The stability of the polymethylene compounds increases up to pentamethylene. There is little difference in stability between this and hexamethylene, but ring structures having seven and eight carbon atoms show progressive decrease in stability. The reason for this was suggested by Baeyer, and was formulated in the following way: —

"The four valences of a carbon atom act parallel to lines forming the corners of a tetrahedron with its center, making angles of 109° 28′ with one another. The direction of the valences can be altered, but any such alteration produces a strain whose amount is proportional to the angle through which the valences are diverted."



The following figures show the angle of deviation necessary for the formation of the ring structure in the several polymethylenes:

Trimethylene	24° 44′
Tetramethylene	9° 44′
Pentamethylene	0° 44′

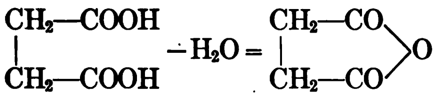
Hexamethylene	−5° 16′
Heptamethylene	−9° 33′
Octamethylene	−12° 51′

The strain is least in the case of pentamethylene among all the cyclo methylene compounds, which corresponds with its stability.

In harmony with the facts mentioned in support of the validity of the " strain theory " is the observation that heptamethylene when heated with bromine in a sealed tube changes to a methyl-substituted hexamethylene ring. These compounds are often called cyclopropane, cyclobutane, cyclopentane, etc.

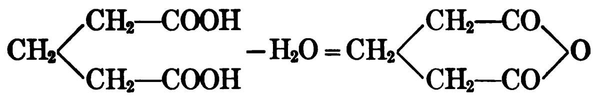
The formation of a ring structure has in itself but little influence upon the properties of the hydrocarbons.

114. Anhydrides of the Dibasic Acids. — Oxalic and malonic acids do not form anhydrides. Succinic and glutaric acids readily lose the elements of a molecule of water from within a single molecule of the acid, forming cyclic anhydrides:



$$\begin{array}{l} CH_2{-}COOH \\ | \\ CH_2{-}COOH \end{array} - H_2O = \begin{array}{l} CH_2{-}CO \\ | \\ CH_2{-}CO \end{array}\!\!\!>O$$

Succinic anhydride



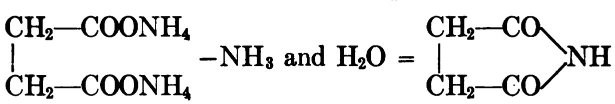
$$CH_2\!\!<\!\begin{array}{l} CH_2{-}COOH \\ CH_2{-}COOH \end{array} - H_2O = CH_2\!\!<\!\begin{array}{l} CH_2{-}CO \\ CH_2{-}CO \end{array}\!\!>O$$

Glutaric anhydride

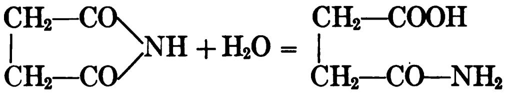
Molecular weight determinations of these anhydrides have shown that the anhydride formation does not take place between two molecules of acid. Simple solution of these anhydrides in water converts them back into the acids from which they were derived.

The failure of the two and three carbon dibasic acids to form anhydrides is in harmony with the "strain theory" (**113**).

115. Succinimide. — When the ammonium salt of succinic acid is heated strongly to the distillation point, a molecule of ammonia and one of water are split off and a ring structure containing the *imide* group =NH is formed:

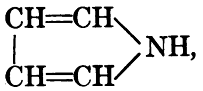


Succinimide is a crystalline compound which melts at 125° and boils at 288°. On warming with barium hydroxide solution it takes on one molecule of water, forming the half amide of succinic acid:

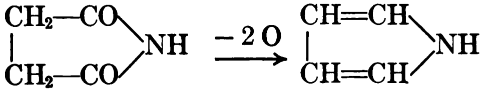


Glutarimide is produced in a similar manner from the ammonium salt of glutaric acid. These are examples of compounds in which nitrogen takes part with carbon in the formation of cyclic compounds.

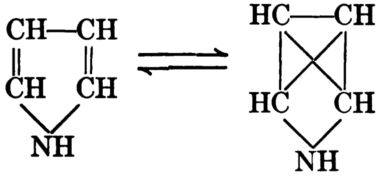
116. Pyrrol,



is formed from succinimide by distilling the latter with zinc dust, which abstracts oxygen:

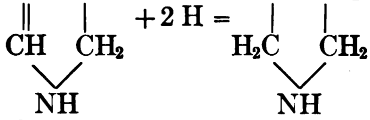


Pyrrol does not take up halogens directly, as would be expected from its possessing two double bonds. This peculiarity of certain cyclic compounds differentiates them sharply from the olefines. Pyrrol can, however, take up two atoms of hydrogen when reduced with acetic acid and zinc dust (nascent hydrogen), and the resulting *Pyrroline*, or *dihydropyrrol*, absorbs two atoms of bromine as do the olefines. This peculiar behavior has led to the assumption that instead of the double bond between the two pairs of carbon atoms one bond from each of the four is directed toward the center of the ring. This form should be very stable as compared with the double bond. The fact that nascent hydrogen is taken up by pyrrol probably finds an explanation in the existence of a small amount of the formula containing the double bond in dynamic equilibrium with the centric formula:


Active modification

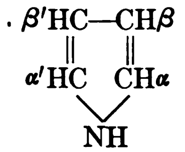
Principal form
Inactive

When two atoms of hydrogen are absorbed the centric formula is changed to one containing a double bond, as in pyrroline:

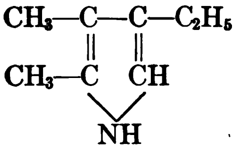

Pyrroline

Pyrrolidine

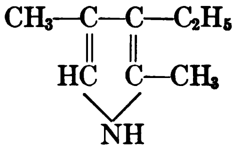
re derivatives of hæmoglobin, the respiratory pigment of the blood. Pyrrol derivatives are present in nicotine, an alkaloid contained in tobacco, and in the alkaloids of the tropine group, *e.g.* atropine, cocaine, etc., and in the bile pigments. The structure of the pyrrol derivatives is indicated thus:



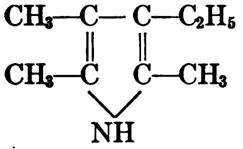
The pyrrol derivatives important from the biological standpoint are the following:



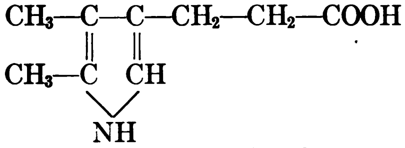
Isohæmopyrrol
β-ethyl, α′-β′-dimethyl pyrrol



Kryptopyrrol
α-methyl-β-ethyl-β′-methyl pyrrol



Phyllopyrrol
α-methyl-β-ethyl-α′-β′-dimethyl pyrrol

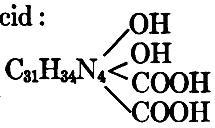


Isophonopyrrol carboxylic acid
β-propionic acid-α′, β′-dimethyl pyrrol

All four of these are derived from *hæmatin,* a substance containing iron which is present in the blood in combination with globin, a protein. The entire complex is called hæmoglobin. This has the power of combining with oxygen in loose combination and thus serves to transport oxygen throughout the body.

Hæmin, $C_{33}H_{32}O_4N_4FeCl$, crystallizes out when defibrinated blood is dropped into a large volume of glacial acetic acid containing some sodium chloride, the solution being heated to 95°. This treatment separates the *hæmatin* from the hæmoglobin, and the compound hæmin which crystallizes out is the hydrochloride of hæmatin. It forms minute bluish black crystals with a metallic luster. It is insoluble in water, alcohol, or ether, but dissolves in chloroform containing quinine or pyridine. From such a solution it crystallizes out when alcohol containing sufficient hydrochloric or acetic acid to neutralize the base (quinine or pyridine) is added.

Hæmin contains two carboxyl groups. It combines with two molecules of hydrobromic acid. The iron becomes loosened in this reaction, and some further unknown change takes place. The dibrom compound when hydrolyzed loses its bromine, the latter being replaced by two hydroxyls. The resulting compound, known as hæmatoporphyrin, is a dihydroxy-dibasic acid:

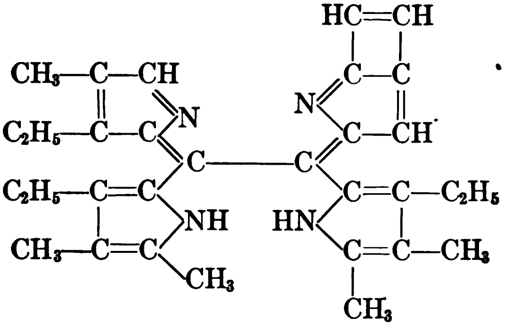


$$C_{31}H_{34}N_4{<}\begin{matrix}OH\\OH\\COOH\\COOH\end{matrix}$$

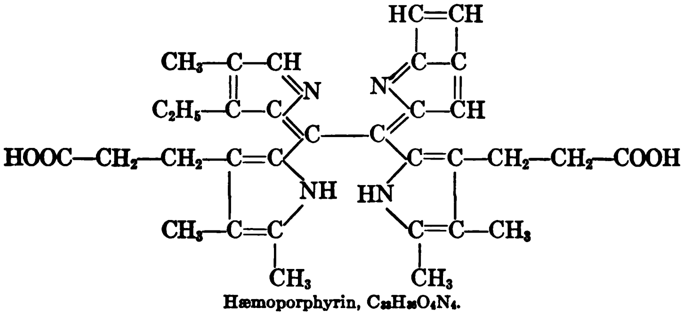
This when heated with methyl alcoholic potassium hydroxide in pyridine solution undergoes reduction and loses two molecules of water:

$$C_{33}H_{38}O_6N_4 + H_2 = C_{33}H_{36}O_4N_4 + 2\,H_2O$$

The product thus obtained is called hæmoporphyrin. It is a dibasic acid. On heating hæmoporphyrin with soda lime (a mixture of CaO and Na_2O) the two carboxyl groups are destroyed, CO_2 being split off, and a new compound, *ætioporphyrin*, is formed. The following formulæ for the last-named derivatives have been proposed by Willstätter:



Ætioporphyrin, $C_{31}H_{36}N_4$



Hæmoporphyrin, $C_{33}H_{36}O_4N_4$.

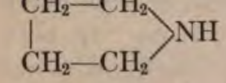
Ætioporphyrin is, according to the researches of Willstätter and his pupils, the mother substance from which both chlorophyll and hæmatin are derived. In both therefore the molecules consist of four substituted pyrrol groups. They assume that the iron in hæmatin is united with nitrogen.

In chlorophyll the condensed pyrrol nucleus possesses two carboxyl groups which are united with two alcohols, methyl alcohol and *phytol*, a secondary alcohol with the formula $C_{20}H_{39}OH$, to form an ester. Instead of iron, chlorophyll contains magnesium linked to nitrogen. A number of decomposition products of both hæmatin and chlorophyll have been described and carefully studied with a view to elucidating their chemical nature, but their description would be beyond the scope of this book. The essential fact to be borne in mind is the close chemical relationship between these plant and animal pigments.

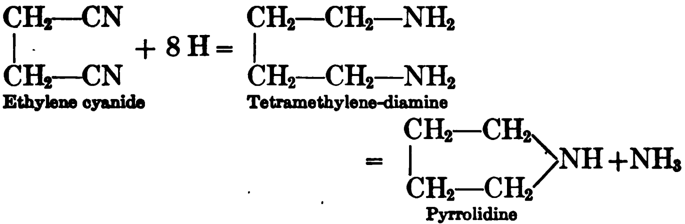
It should be pointed out as an interesting biological fact that carefully conducted feeding experiments with laboratory animals have shown that neither chlorophyll nor hæmatin is an essential constituent of the diet. The animal body is able to construct the red respiratory pigment from certain of the amino acids yielded by the proteins of the food. Probably those containing the pyrrol ring are of particular importance for this purpose.

The bile acids, bilirubin and biliverdin, are derived from disintegrated red corpuscles and are derivatives of condensed pyrrol nuclei which have their origin in the hæmatin complex of the hæmoglobin.

117. **Pyrrolidine** is of great biological interest since its derivatives, *proline* (α-pyrrolidine carboxylic acid) and *oxyproline* (α-oxypyrrolidine carboxylic acid), occur among the amino acids which result from the hydrolysis of proteins.



In addition to the method described for preparing pyrrolidine (116), another which confirms its structure is its formation from ethylene cyanide. When treated with sodium and alcohol, the nascent hydrogen formed induces the following series of changes:



$$\begin{array}{l} CH_2—CN \\ | \\ CH_2—CN \end{array} + 8\,H = \begin{array}{l} CH_2—CH_2—NH_2 \\ | \\ CH_2—CH_2—NH_2 \end{array}$$

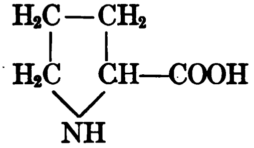
Ethylene cyanide

Tetramethylene-diamine

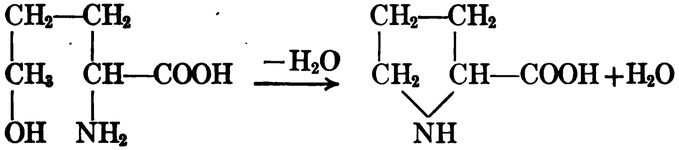
Pyrrolidine

Pyrrolidine boils at 87°.

118. Proline, *a-pyrrolidine carboxylic acid,*

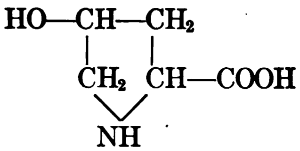


is a product of the hydrolysis of many proteins of both animal and plant origin. l-proline is the form occurring in nature. Its structure is made evident by its synthesis from a-amino δ-oxyvalerianic acid. This on heating loses a molecule of water and forms proline:



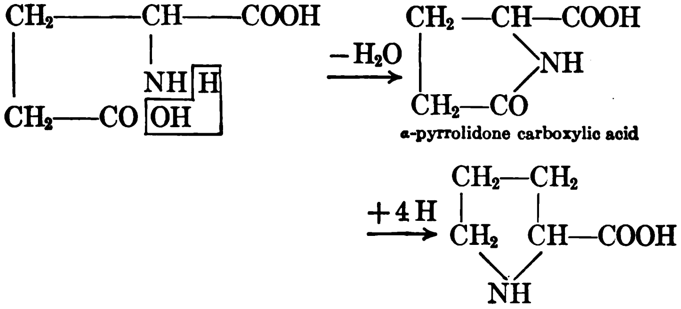
Proline is easily soluble in water. It is the only one of the naturally occurring amino acids which is readily soluble in absolute alcohol. The blue copper salt is likewise soluble in alcohol, and this salt is made use of in the purification. Racemic proline, the mixture of equal parts of the two optical forms, forms a copper salt which is violet when dry but absorbs moisture from the air and becomes blue again. Proline forms a salt with picric acid (**184**) which is useful in its identification. Among the proteins hordein of barley yields the largest amount of this amino acid.

119. Oxy-Proline, *β-oxy-α-pyrrolidine carboxylic acid,*



occurs in gelatin. It decomposes at 270° with foaming. The vapors evolved give the reactions of pyrrol (**116**).

120. Pyrrolidone Carboxylic Acid. — Of theoretical interest is the property of glutamic acid (**106**) of separating a molecule of water when heated to 185–190° with the formation of a ketone derivative of proline:

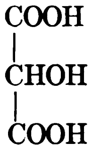


CHAPTER XI

HYDROXY AND KETONE ACIDS

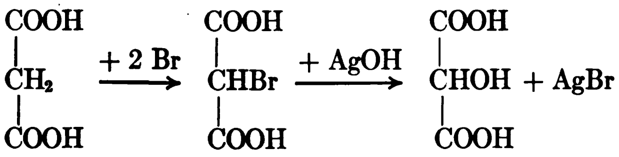
Hydroxy Dibasic Acids

121. Tartronic Acid. — The simplest member of the series of dibasic hydroxy acids is tartronic acid,



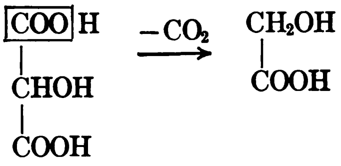
$$\begin{array}{c} COOH \\ | \\ CHOH \\ | \\ COOH \end{array}$$

This acid does not occur in nature. It is formed from malonic acid by the following reactions:



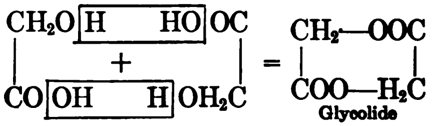
$$\begin{array}{c} COOH \\ | \\ CH_2 \\ | \\ COOH \end{array} \xrightarrow{+ 2\,Br} \begin{array}{c} COOH \\ | \\ CHBr \\ | \\ COOH \end{array} \xrightarrow{+ AgOH} \begin{array}{c} COOH \\ | \\ CHOH \\ | \\ COOH \end{array} + AgBr$$

Tartronic acid melts at 187° with the loss of carbon dioxide:



$$\begin{array}{c} \boxed{COO}H \\ | \\ CHOH \\ | \\ COOH \end{array} \xrightarrow{-CO_2} \begin{array}{c} CH_2OH \\ | \\ COOH \end{array}$$

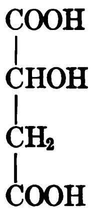
The glycolic acid formed at this temperature at once reacts with a second molecule to form an ester called *glycolide.*



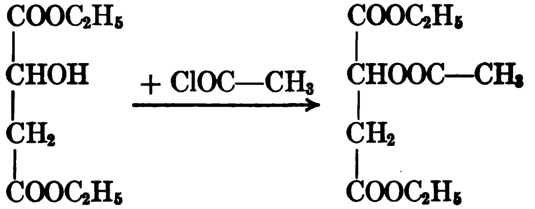
$$\begin{array}{l} CH_2O\boxed{H \quad HO}OC \\ | \qquad + \qquad | \\ CO\boxed{OH \quad H}OH_2C \end{array} = \begin{array}{l} CH_2-OOC \\ | \qquad\quad | \\ COO-H_2C \end{array}$$

Glycolide

122. Malic Acid, ***hydroxysuccinic acid,*** is present in various unripe fruits, as apples, pears, etc. It is best prepared from unripe mountain ash berries or from rhubarb stalks. Its structure is indicated by its conversion into chlorsuccinic acid by treatment with phosphorus pentachloride, and by the fact that the alcohol group in succinic ester reacts with acetyl chloride, forming an acetyl derivative:



$$\begin{array}{l} COOH \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOH \end{array}$$



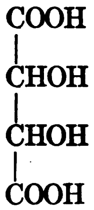
$$\begin{array}{l} COOC_2H_5 \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{+ ClOC-CH_3} \begin{array}{l} COOC_2H_5 \\ | \\ CHOOC-CH_3 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array}$$

On boiling the juice of rhubarb or of mountain ash berries with milk of lime, calcium malate is precipitated, since it is relatively insoluble. The salt is washed, dried, and weighed, and is then treated with the calculated amount of sulphuric acid. Insoluble calcium sulphate separates out. The solution containing the malic acid is evaporated to the point of crystallization.

Malic acid is readily soluble in water, alcohol, and ether. The calcium salt is precipitated from dilute water solutions by the addition of alcohol. Like normal calcium butyrate (**70**) it is more soluble in cold water than in hot and is precipitated from concentrated solutions on boiling.

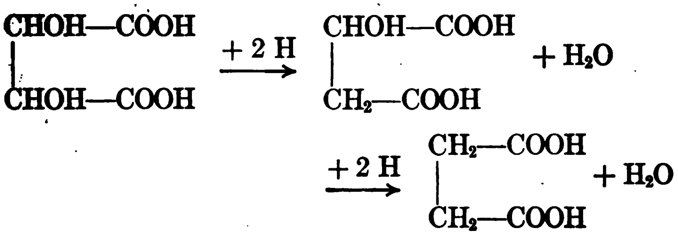
Since malic acid contains an asymmetric carbon atom it exists in two isomeric forms which differ only with respect to their behavior toward polarized light. (See amyl alcohol.) The natural form is l-malic acid. When malic acid is heated to 180°, it loses a molecule of water and forms maleic and fumaric acids. These possess a double bond, COOH—CH=CH—COOH. They will be treated later (**133**).

123. Tartaric Acids, *dihydroxy succinic acid.*



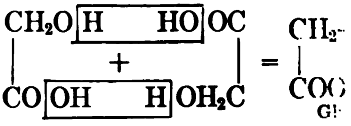
$$\begin{array}{l} \mathrm{COOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{COOH} \end{array}$$

There are four acids having this composition. They all react with PCl_5 to give dichlor succinic acid, and when reduced by heating with hydriodic acid they yield in turn malic and succinic acids.



$$\begin{array}{l} \mathrm{CHOH{-}COOH} \\ | \\ \mathrm{CHOH{-}COOH} \end{array} \xrightarrow{+2\,\mathrm{H}} \begin{array}{l} \mathrm{CHOH{-}COOH} \\ | \\ \mathrm{CH_2{-}COOH} \end{array} + H_2O$$

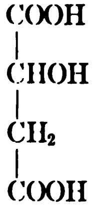
$$\xrightarrow{+2\,\mathrm{H}} \begin{array}{l} \mathrm{CH_2{-}COOH} \\ | \\ \mathrm{CH_2{-}COOH} \end{array} + H_2O$$



$$\begin{array}{l} CH_2O\boxed{H\quad HO}OC \\ |\qquad\quad +\qquad\quad | \\ CO\boxed{OH\quad H}OH_2C \end{array} = \begin{array}{l} CH_2- \\ | \\ COO \end{array}$$

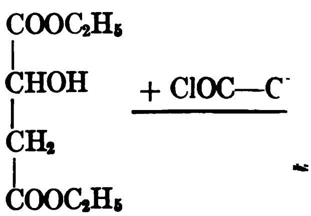
ence of two
which makes
actic acids.)
atoms in a

122. Malic Acid, *hydroxysuccinic* … and must exist,



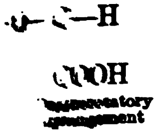
$$\begin{array}{l} COOH \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

various unripe fruits, as … form, an inactive
It is best prepared fro… r inactive lactic
ash berries or from … rms, and a fourth
structure is indicated b… inactive, in which
chlorsuccinic acid by … on atom is the
phorus pentachloride. … ame molecule, *i.e.*
the alcohol group in succinic e… ompensated. It is
chloride, forming an acetyl deriv… ly two configura-



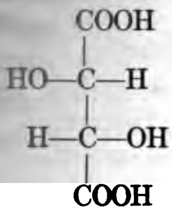
$$\begin{array}{l} COOC_2H_5 \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{+\ ClOC—C}$$

mode of arrange-
form, but if we
of one configu-
grouping represents
represent the oppo-



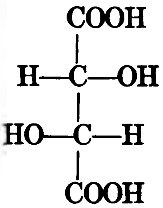
On boiling the juice of r…
berries with milk of lime, c…
since it is relatively insolub…
and weighed, and is then …
amount of sulphuric acid. …
separates out. The solu… so as to be united
evaporated to the point o… the entire complex
Malic acid is readily s… II will be dextro-
ether. The calcium salt is … molecule will
solutions by the addition … the plane of

light, and an inactive compound results. This called *mesotartaric acid* to differentiate it from the ic form, which consists of both the d- and l- acids qual amounts. Mesotartaric acid cannot be separated o d- and l-tartaric acids as can the racemic tartaric id.



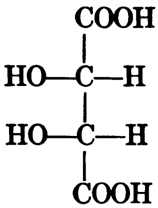
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{COOH}\end{array}$$

I



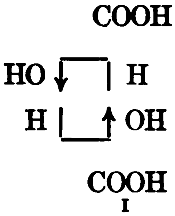
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{COOH}\end{array}$$

II



$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{COOH}\end{array}$$

III



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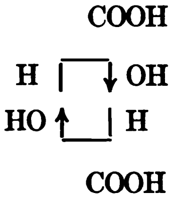
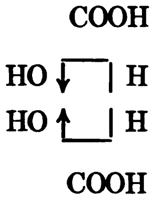


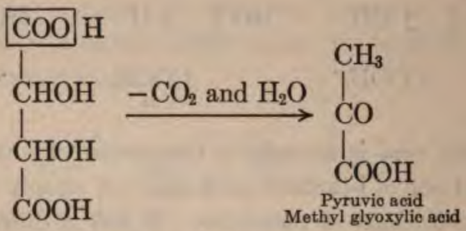
II



III

Racemic acid is actually a compound of one molecule of d- and one of l-tartaric acids and not simply a mixture of the two kinds of molecules. It has a different crystalline form from the two active acids, and the crystals carry water of crystallization. The racemic acid crystals are much less soluble in water than are the active acids, and have a higher melting point. The union is however a feeble one, and in solution it exists as separate molecules of the optically active acids. This is indicated by the fact that the molecular weight as shown by the freezing point and boiling point methods corresponds to the formula $C_4H_6O_6$. The esters of tartaric acids are volatile, and their vapor densities correspond to the single instead of to double molecules. Crystals of racemic acid have the composition $2\ C_4H_6O_6 + 2\ H_2O$. d- and l-tartaric acids crystallize without water of crystallization.

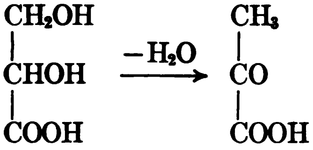
Dextro- and *levo-tartaric acids* melt at 170°. 100 parts of water at 20° C. dissolve 139.44 parts, and at 100° 343.35 parts of either the d- or l- acids. They are much less soluble in alcohol and insoluble in ether. Tartaric acid when strongly heated with a dehydrating agent such as potassium bisulphate loses water and carbon dioxide and there distills over a ketone acid, *pyruvic acid*. This acid is likewise known as *pyroracemic acid* and as *methyl glyoxylic acid* (**67**).



$$\begin{array}{l} \boxed{COO}\,H \\ | \\ CHOH \\ | \\ CHOH \\ | \\ COOH \end{array} \xrightarrow{-CO_2 \text{ and } H_2O} \begin{array}{l} CH_3 \\ | \\ CO \\ | \\ COOH \end{array}$$

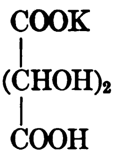
Pyruvic acid
Methyl glyoxylic acid

Pyruvic acid has great biological interest. It will be further considered in connection with carbohydrate metabolism and the synthesis of fats. It is probable that the first step in the decomposition is the loss of carbon dioxide and the formation of *glyceric acid* which then loses a molecule of water. Glyceric acid itself when heated is converted into pyruvic acid.

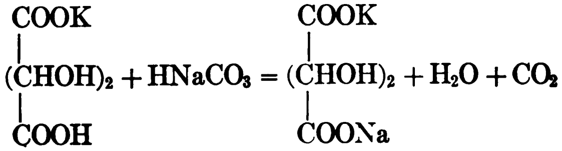


$$\begin{array}{l} \mathrm{CH_2OH} \\ | \\ \mathrm{CHOH} \\ | \\ \mathrm{COOH} \end{array} \xrightarrow{-H_2O} \begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CO} \\ | \\ \mathrm{COOH} \end{array}$$

The acid potassium salt of d-tartaric acid crystallizes out of wine as alcohol accumulates during fermentation. The crude salt is known as *argol* and contains some calcium tartrate and coloring matters. The acid potassium salt is dissolved in hot water, leaving the calcium salt behind, and after treatment with animal charcoal to remove coloring matters the solution is allowed to cool and crystallize. This salt is then known as *cream of tartar*. It is very sparingly soluble in water and still less so in alcohol. It is extensively used in baking powders. Here it is mixed with sodium bicarbonate, with which it reacts when dissolved to form sodium potassium tartrate or *Rochelle salt:*



$$\begin{array}{l} \mathrm{COOK} \\ | \\ \mathrm{(CHOH)_2} \\ | \\ \mathrm{COOH} \end{array}$$

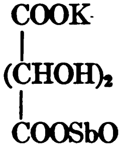


$$\begin{array}{l} \mathrm{COOK} \\ | \\ \mathrm{(CHOH)_2} \\ | \\ \mathrm{COOH} \end{array} + HNaCO_3 = \begin{array}{l} \mathrm{COOK} \\ | \\ \mathrm{(CHOH)_2} \\ | \\ \mathrm{COONa} \end{array} + H_2O + CO_2$$

Rochelle salt

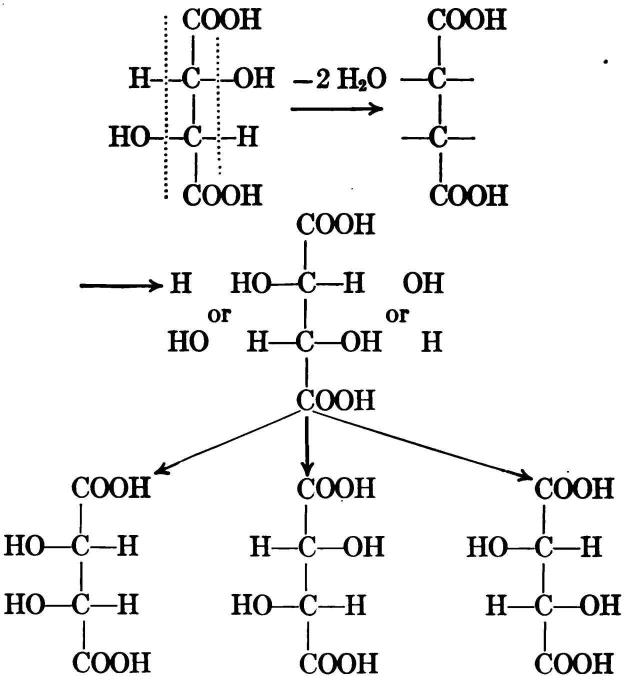
The carbon dioxide being generated throughout the dough causes it to rise into a spongy condition. Baking powders are therefore a substitute for yeast.

Dipotassium tartrate, $C_4H_4O_6K_2$, is readily soluble in water. Acid potassium tartrate dissolves antimony oxide, SbO, to form potassium antimonyl tartrate or tartar emetic:



$$\begin{array}{l} \mathrm{COOK} \\ | \\ (\mathrm{CHOH})_2 \\ | \\ \mathrm{COOSbO} \end{array}$$

Racemic acid and mesotartaric acid are both formed from d-tartaric acid by boiling with sodium hydroxide. This is explained by the assumption that water is alternately separated and added.



Mesotartaric acid d-tartaric acid l-tartaric acid

According to the law of chance, if water is split off from a compound and added on again in the way described, an OH group will take the place of H, just as frequently as it will replace the separated OH. Thus on repeating the separation and addition of water a sufficient number of times a state of equilibrium will be established in which all possible arrangements of H and OH groups will exist in the solution. Such a conception helps to make clear the process of racemization and likewise the transformation of certain sugars into others.

SEPARATION OF RACEMIC SUBSTANCES INTO THEIR OPTICALLY ACTIVE CONSTITUENTS

Optically active isomers show no differences in their solubility, melting point, boiling point, or amount of water of crystallization. They differ only with respect to their effect in twisting the ray of polarized light. Ordinary methods of separating mixtures depend on differences of physical or chemical properties, so that for the separation of optical isomers special procedures had to be devised. Three general methods for accomplishing such separations are known, and all of these were discovered by the brilliant French chemist, Pasteur.

The first of these depends upon the property possessed by sodium ammonium racemate, when allowed to crystallize at temperatures below 28°, of depositing side by side the sodium ammonium salt of dextro- and of levo-tartaric acids. These crystals possess hemihedral faces, and are, like mirror images, not superimposable. They

and separated by
hand. On pre-
of crystals and
are found to have
the two solutions

combining the d-
active base. The
alike in their con-
physical proper-
fractional crystal-
cinchonine, brucine,
and are useful in such
acids. When the
base an optically

Pasteur for obtaining
mixture depends
two forms of the
appreciable biological
animal and plant
of optically active
form of each occurs in
optically active sub-
present in a racemic
is able to use as a
one optical form
infrequently one of
nutrient. Pasteur
cum could make

use of the ammonium salt of d-tartaric acid but not the l- form. (See lactic acid.) Obviously this method is available only for obtaining the isomer which does not occur in nature.

Trihydroxy Glutaric Acids, COOH—CHOH—CHOH—CHOH—COOH. — There are four possible isomers having this structure. They result from the oxidation of the sugars and will be treated more in detail later (**152**).

Tetrahydroxy Dibasic Acids, $COOH—(CH_2OH)_4COOH$, likewise are important oxidation products of the sugars. The most important are *saccharic acid, mucic acid,* and *isosaccharic acids.*

124. Oxybutyric Acid and Its Related Compounds. — The condensation of two molecules of acetaldehyde to form β-oxybutyric aldehyde or "aldol" has been described (**32**). Like other aldehydes this is oxidizable to an acid of the same number of carbon atoms, β-oxybutyric acid:

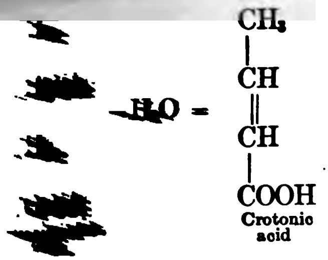
$$CH_3—CHOH—CH_2—CHO \xrightarrow{+O} CH_3—CHOH—CH_2—COOH$$

This acid has one asymmetric carbon atom and so exists in three stereoisomeric forms, dextro, levo, and inactive, of which the levorotatory form is of the greatest physiological interest since it occurs in the urine in diabetes, sometimes in surprising quantities, more than a hundred and fifty grams a day having been observed.

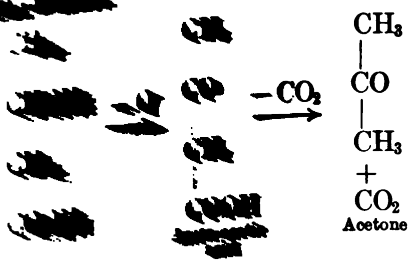
l-β-oxybutyric acid closely resembles lactic acid in its behavior. It is an odorless and colorless sirup, non-

[redacted] tained in the crystal- unstable. It is readily and acetic ether, but ether. Its salts are soluble in alcohol, and the addition of ether. detection. It consists of

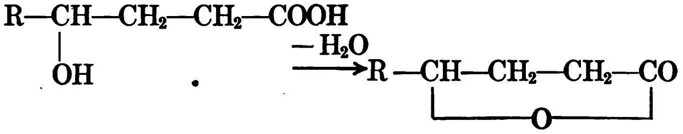
sulphuric acid β-oxy- crotonic acid:



[redacted] it yields the ketone acid, breaks down into acetone [redacted]



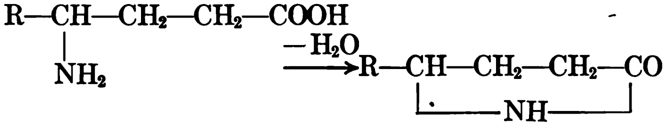
[redacted]—CH₂—CH₂—COOH, [redacted] with the formation [redacted] of internal esters called lactones. This tendency is so pronounced that many acids of this type are not known in the free state, but only as salts, esters, etc. On being set free they at once pass into the cyclic structure. Alkalies convert lactones back into the salts of the γ-hydroxy acids. The same conversion is in part effected by boiling with water.



$$\underset{\mathrm{OH}}{\mathrm{R{-}CH}}\mathrm{{-}CH_2{-}CH_2{-}COOH} \xrightarrow{-H_2O} \mathrm{R{-}\underbrace{CH{-}CH_2{-}CH_2{-}CO}_{O}}$$

Lactone

126. γ-Amino Acids show the same tendency to lose water and form cyclic compounds. These are known as lactams:



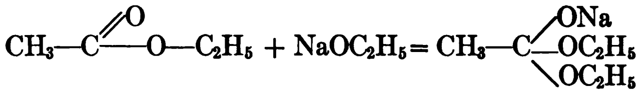
$$\underset{\mathrm{NH_2}}{\mathrm{R{-}CH}}\mathrm{{-}CH_2{-}CH_2{-}COOH} \xrightarrow{-H_2O} \mathrm{R{-}\underbrace{CH{-}CH_2{-}CH_2{-}CO}_{NH}}$$

Lactam

127. Aceto-acetic Acid, CH_3—CO—CH_2—COOH, possesses great physiological interest since it occurs in the blood and urine in diabetes, where it results from the oxidation of β-oxybutyric acid. It is a very unstable, strongly acid sirup which absorbs moisture readily from the air. On warming it decomposes into acetone and carbon dioxide as illustrated above. In the tissues β-oxybutyric acid results from the oxidation of fat and in small amount from protein decomposition. This acid is particularly difficult for the diabetic to oxidize, although the normal organism is able to accomplish it. β-oxybutyric acid is partly oxidized to aceto-acetic acid in the blood and the decomposition of the latter acid into acetone and carbon dioxide takes place spontaneously, so that in the severe diabetic blood there are always found the three compounds, β-oxybutyric and aceto-acetic acids and acetone, together.

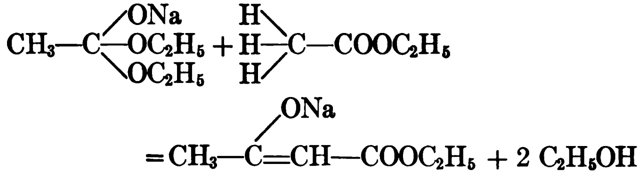
A certain peculiarity in the isomerism displayed by aceto-acetic acid, together with the great importance of its ester in synthesis, make it desirable to describe the behavior of the latter in some detail.

Aceto-acetic Ester is formed by the reaction of ethyl acetate with sodium ethylate. There are three stages to the reaction: the formation of an addition product between ethyl acetate and sodium ethylate:

(1)


$$CH_3-\overset{\displaystyle O}{\overset{\|}{C}}-O-C_2H_5 + NaOC_2H_5 = CH_3-\overset{\displaystyle ONa}{\underset{\displaystyle OC_2H_5}{C}}-OC_2H_5$$

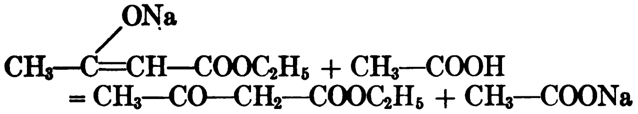
This then reacts with a second molecule of ethyl acetate to form the sodium compound of aceto-acetic ester:

(2)


$$CH_3-\overset{\displaystyle ONa}{\underset{\displaystyle OC_2H_5}{C}}-OC_2H_5 + \overset{\displaystyle H}{\underset{\displaystyle H}{H-C}}-COOC_2H_5$$

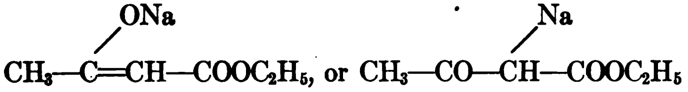
$$= CH_3-\overset{\displaystyle ONa}{C}=CH-COOC_2H_5 + 2\ C_2H_5OH$$

The ethyl aceto-acetate is formed on treating the sodium compound with an acid. This is known as Claisen's synthesis:

(3) 

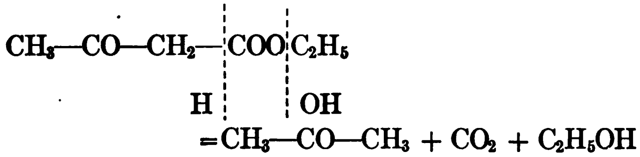
$$CH_3{-}\overset{ONa}{C}{=}CH{-}COOC_2H_5 + CH_3{-}COOH$$
$$= CH_3{-}CO{-}CH_2{-}COOC_2H_5 + CH_3{-}COONa$$

The sodium derivative, as will appear later, may have either of the two following structures:

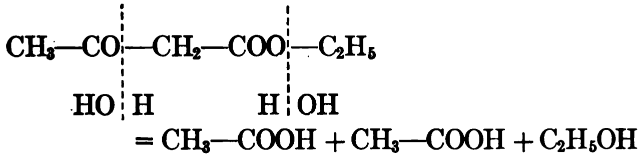


$$CH_3{-}\overset{ONa}{C}{=}CH{-}COOC_2H_5, \text{ or } CH_3{-}CO{-}\overset{Na}{C}H{-}COOC_2H_5$$

Aceto-acetic ester undergoes decomposition in two ways according to the conditions to which it is subjected. Dilute alkalies or acids on warming decompose it into a ketone, alcohol, and carbon dioxide. This is known as the *ketone decomposition* (*a*). When it is decomposed by a strong solution of alcoholic potassium hydroxide the ester suffers *acid decomposition* (*b*).

(*a*) 

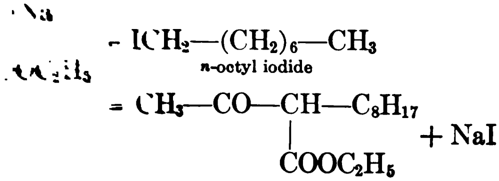
$$CH_3{-}CO{-}CH_2{-}\underset{H}{\vdots}\,COO\,\underset{OH}{\vdots}\,C_2H_5$$
$$= CH_3{-}CO{-}CH_3 + CO_2 + C_2H_5OH$$

(*b*) 

$$CH_3{-}CO\,\underset{HO\ H}{\vdots}{-}CH_2{-}COO\,\underset{H\ OH}{\vdots}{-}C_2H_5$$
$$= CH_3{-}COOH + CH_3{-}COOH + C_2H_5OH$$

The great importance of aceto-acetic acid in synthesis lies in the fact that the sodium in sodio-aceto-acetic ester can be substituted by various radicals, after which the types of decomposition described above yield ketones or acids.

aceto-acetic ester reacts with n-octyl group replaces the sodium. On acid compound yields capric acid,



$$+ ICH_2—(CH_2)_6—CH_3$$

n-octyl iodide

$$= CH_3—CO—\underset{COOC_2H_5}{CH}—C_8H_{17} + NaI$$

$$C_8H_{17}$$

$$COOC_2H_5$$

$$CH_3—(CH_2)_8—COOH + C_2H_5OH$$

Capric acid Alcohol

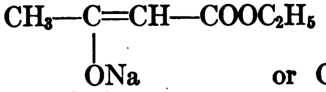
when subjected to the ketone methyl-nonyl-ketone:

$$C_9H_{19} + CO_2 + C_2H_5OH$$

methyl-nonyl-ketone

ketones have been readily

As was stated above, sodio-aceto-acetic ester may have either of two structures:



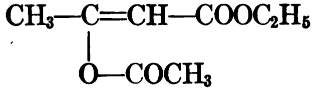
$$\begin{array}{l} CH_3{-}C{=}CH{-}COOC_2H_5 \\ \quad\;\; | \\ \quad\; ONa \end{array}$$

Enol form

or $CH_3{-}CO{-}CHNa{-}COOC_2H_5$

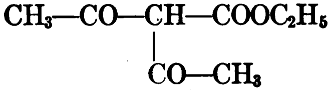
Keto form

When an acid chloride reacts with sodio-aceto-acetic ester, it is possible to obtain at will a compound in which the acetyl group is linked directly to carbon or through oxygen to carbon.



$$\begin{array}{l} CH_3{-}C{=}CH{-}COOC_2H_5 \\ \quad\;\; | \\ \quad\; O{-}COCH_3 \end{array}$$

O-derivative
(Insoluble in alkali)



$$\begin{array}{l} CH_3{-}CO{-}CH{-}COOC_2H_5 \\ \qquad\qquad\; | \\ \qquad\quad\; CO{-}CH_3 \end{array}$$

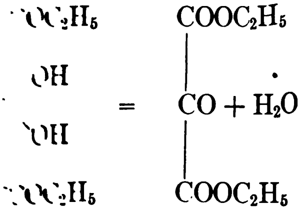
C-derivative
(Soluble in alkali)

When the sodio-aceto-acetic ester is treated directly with acetyl chloride, the C-derivative only is formed. This compound is soluble in alkali since the hydrogen in the CH group is linked to three negative radicals, two acetyl and one carbethoxyl groups. (Compare malonic ester.) When, however, the aceto-acetic ester is mixed with pyridine and the acetyl chloride added to the mixture, the O-derivative only is formed.

As a general rule the solubility in alkali of such derivatives as result from the condensation of halogen compounds with metallic compounds of substances which show tautomerism is accepted as evidence of the formation of the C type of derivative, since solubility in alkali should be expected where there is an active hydrogen atom which would permit the formation in alkali of a sodium or potassium derivative.

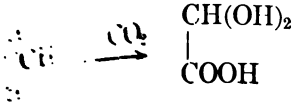
Th h compounds has
iodi n the keto into the
dec y even in solution,
C. H and is stable except
CH the *enol* form gives
ic chloride and that
es as an easy test for

malonic ester is boiled
CH lution, the two bromine
hydroxyl groups:



$$COOC_2H_5 \quad OH \quad OH \quad COOC_2H_5 = COOC_2H_5 - CO - COOC_2H_5 + H_2O$$

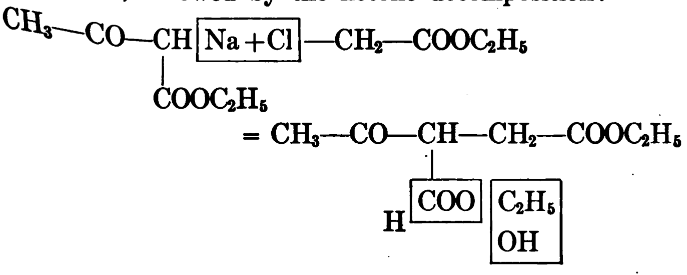
f the ability of one car-
groups when it is in close
dicals (compare glyoxylic
oxalic acid is consider-
acid, for on boiling with
and forms glyoxylic



$$\xrightarrow{} CH(OH)_2 - COOH$$

Mesoxalic acid is of biological interest owing to its relation to the formation of *alloxan* (**140**).

129. Levulinic Acid, $CH_3—CO—CH_2—CH_2—COOH$, is a γ-ketonic acid of interest because it is formed by the decomposition of sugars by means of strong hydrochloric acid. Its structure is revealed by its formation by the condensation of sodio-aceto-acetic ester with chloracetic acid ester, followed by the ketone decomposition:



$$\underset{\displaystyle COOC_2H_5}{CH_3—CO—CH}\boxed{Na+Cl}—CH_2—COOC_2H_5$$

$$= CH_3—CO—\underset{\displaystyle H\boxed{COO}\boxed{\begin{matrix}C_2H_5\\ OH\end{matrix}}}{CH}—CH_2—COOC_2H_5$$

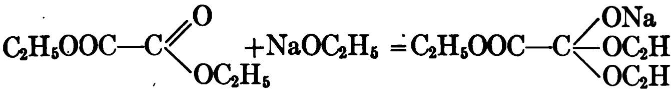
$$= CH_3—CO—CH_2—CH_2—COOC_2H_5$$

Levulinic ethyl ester

Levulinic acid is crystalline. It melts at 33.5° and boils with some decomposition at 250°. It behaves like the typical ketones in yielding an oxime, a cyanhydrin, and a hydrazone (**37**).

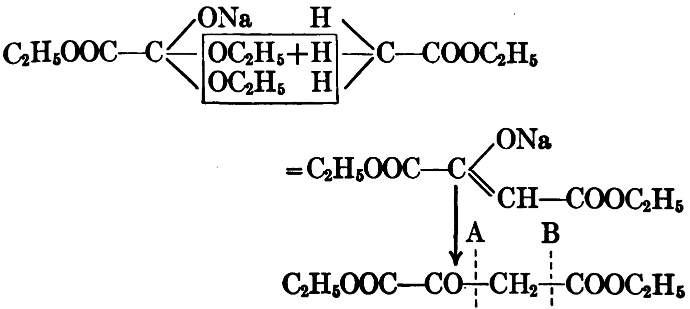
Levulinic acid when ingested in amounts above five to six grams is excreted unchanged in the urine.

130. Oxalacetic Acid is obtained through the Claisen synthesis by the condensation of ethyl oxalate with ethyl acetate in the presence of sodium ethylate (**127**).



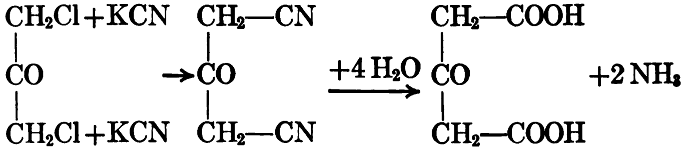
$$C_2H_5OOC—C\begin{cases}\!=O\\ —OC_2H_5\end{cases} + NaOC_2H_5 = C_2H_5OOC—C\begin{cases}—ONa\\ —OC_2H_5\\ —OC_2H_5\end{cases}$$

Diethyl oxalate Addition product



Like aceto-acetic ester oxalacetic ester can hydrolyze in two ways (**127**) at the points indicated by A and B. The first is accomplished by treatment with alkalies and yields oxalic and acetic acids; the second is effected by the action of dilute sulphuric acid and leads to the formation of pyruvic ester (**67**), carbon dioxide and alcohol.

131. Acetone Dicarboxylic Acid, $COOH—CH_2—CO—CH_2—COOH$, results from the nitrile formed by the action of potassium cyanide upon symmetrical dichloracetone:

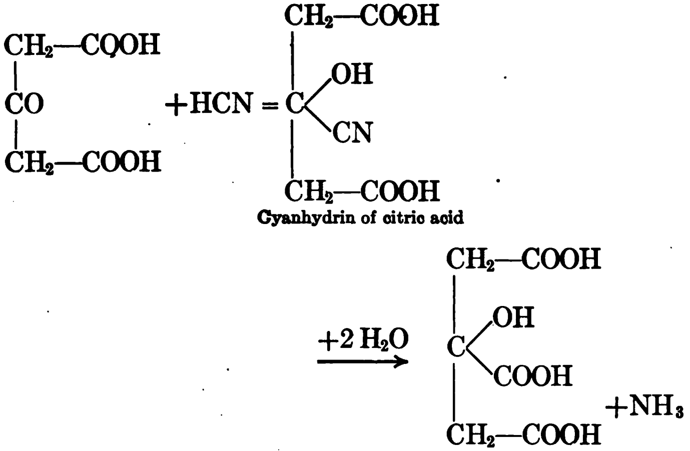


$$\begin{array}{llll} CH_2Cl+KCN & CH_2—CN & & CH_2—COOH \\ | & | & & | \\ CO & \rightarrow CO & \xrightarrow{+4\,H_2O} & CO \qquad +2\,NH_3 \\ | & | & & | \\ CH_2Cl+KCN & CH_2—CN & & CH_2—COOH \end{array}$$

Dichlor acetone — Acetone dicyanide — Acetone dicarboxylic acid

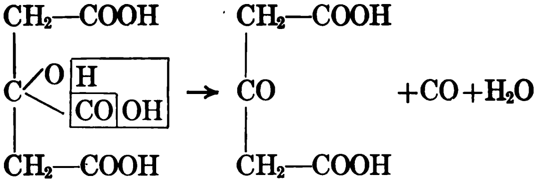
It is also formed by the action of strong dehydrating agents upon *citric acid,* a fact which gives a clue to the structure of the latter acid. Citric acid is formed from acetone dicarboxylic acid by the addition of hydrocyanic acid and subsequent hydrolysis of the oxynitrile.

132. Citric Acid.—As stated above, the nitrile of citric acid is formed by the cyanhydrin formation from acetone dicarboxylic acid:



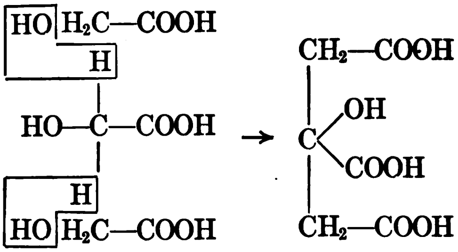
Cyanhydrin of citric acid

The reverse reaction by which citric acid is converted into acetone dicarboxylic acid by dehydrating agents is as follows:



Citric acid occurs in the juice of many plants, especially in lemon juice, from which five per cent or more may be obtained, and in gooseberries, which contain about one per cent. It is also a normal constituent of the milk of animals, but it is not certain whether it comes from the food or is the product of the milk glands. It has also been detected in certain grains, and is therefore one of the most widely distributed compounds in nature. It crystallizes with one molecule of water in large colorless prisms. When it loses its water of crystallization through heating, it forms a fine white powder.

It is formed by the fermentative action of certain bacteria and molds, but the nature of the chemical process by which it is produced from sugars is not clear, since the sugars all contain the normal carbon chain whereas citric acid contains a branched carbon chain. It has been suggested that citric acid may result in fermentation by the condensation with loss of water from three molecules of glycolic acid:



Three molecules of glycolic acid   Citric acid

CHAPTER XII

UNSATURATED DIBASIC ACIDS

Maleic and Fumaric Acids and Their Isomerism

133. There appears to be good evidence that two carbon atoms bound together by a single bond are able to rotate freely about their common axis. Thus only one ethylene chloride, $CH_2Cl—CH_2Cl$, is known. If free rotation of the carbon atoms in Figure 20 were not possible we should expect three modifications of this compound to exist:

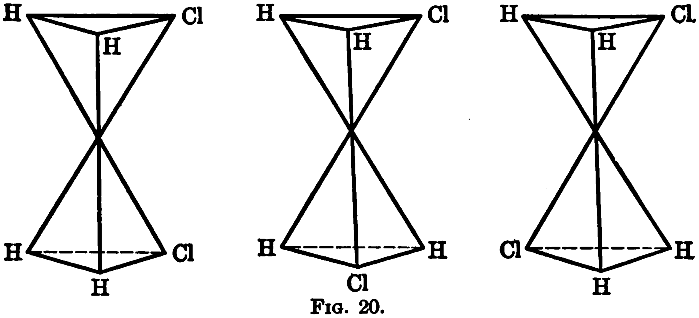


Fig. 20.

If, however, free rotation of the carbon atoms about their common axis is assumed, the three arrangements of the chlorine atoms represent phases of intramolecular movement and not stable positions of the tetrahedra. It is not necessary to assume a continuous movement of rotation. In fact we should expect t arrangement of the atoms would be more other, and that if the atoms were arran whatever they would return to the stal any movement within the molecule wo oscillation about the stable position (8

Such freedom of motion of one car spect to another is in part lost when t

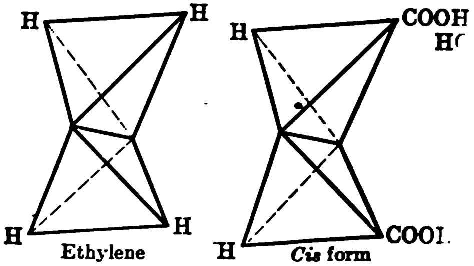
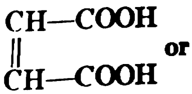


Fig. 21. — Maleic and Fum

established, as was pointed out in di of the crotonic acids (**86**). Assumi the double bond the tetrahedra carbon atoms are in the position their having one edge in conta represented by Figure 21. In suc expect two modifications of ethy



$$\begin{array}{l} CH—COOH \\ \| \\ CH—COOH \end{array}$$

or HO

The carboxyl groups may be ar opposite sides of the molecule.

i-

e.

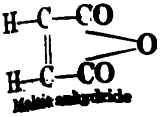
i. That

succinic acid.

. That derived from

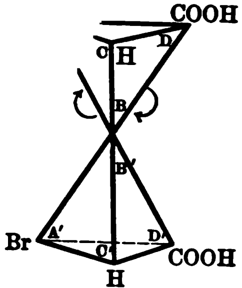
d, and is much more

an anhydride, it would
sitions which the COOH
the most probable one is
This separation should
of water from the two
acid the *trans* structure
erefore the *cis* form.



Maleic anhydride

tion which confirms the these acids is the fol- s add two atoms of



Isodibrom succinic acid
FIG. 23.

above the dibrom addition products he mechanism of this addition in the

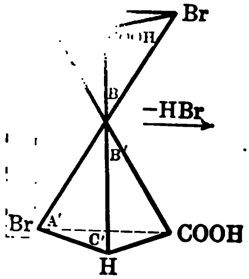
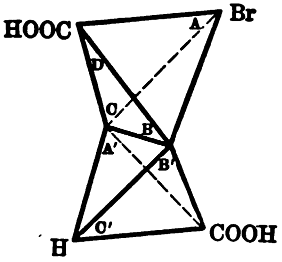


FIG. 24.



Brom fumaric acid
FIG. 25.

se of maleic acid is made clear from an inspection of gures 22–25.

The addition of bromine may take place at A and A′ at B and B′. In either case the same compound would

CHAPTER XIII

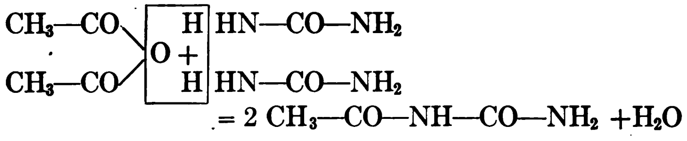
THE UREIDES

Ureides of the Monobasic Acids

134. Acetyl Urea. — Urea, which was treated as the amide of carbamic acid (**57**) (amino formic acid) may also be regarded as a substituted ammonia in which a hydrogen atom of ammonia is replaced by NH_2—CO. Urea does in fact form a series of compounds in which it acts as does ammonia; thus it reacts with acid chlorides forming acetyl, propionyl, etc., ureas:

$$CH_3\text{—}CO\text{—}Cl + HHN\text{—}CO\text{—}NH_2$$
$$= \underset{\text{Acetyl urea}}{CH_3\text{—}CO\text{—}NH\text{—}CO\text{—}NH_2} + HCl$$

The same derivatives are formed by the action of urea on acid anhydrides:

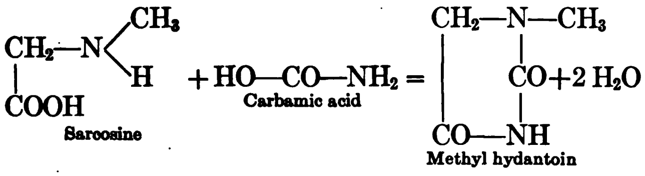


$$\left.\begin{array}{l}CH_3\text{—}CO\\ \\ CH_3\text{—}CO\end{array}\right\rangle \boxed{\begin{array}{r}H\\ O+\\ H\end{array}} \begin{array}{l}HN\text{—}CO\text{—}NH_2\\ \\ HN\text{—}CO\text{—}NH_2\end{array}$$
$$= 2\,CH_3\text{—}CO\text{—}NH\text{—}CO\text{—}NH_2 + H_2O$$

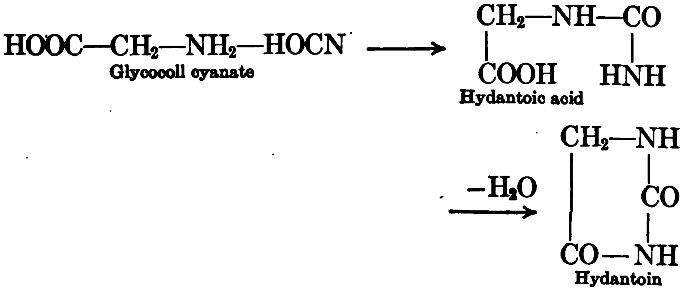
These compounds are solids. Acetyl urea forms silky needles melting at 214°. It is easily soluble in water and alcohol.

Diacetyl Urea, CH_3—CO—NH—CO—NH—CO—CH_3, is formed by the action of carbonyl chloride on acetamide:

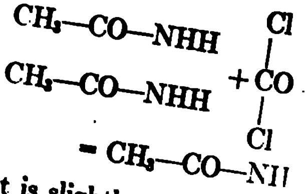
case to a considerable extent with the optical form not found in nature, or are completely burned to carbon dioxide, water, and ammonia. In the case of methyl-amino-acetic acid (sarcosine) (**63**) a part is combined with urea with the formation of methyl hydantoin, the latter appearing in the urine. The mode of formation is probably as follows:



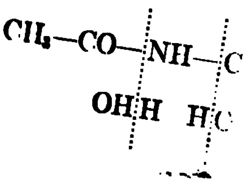
136. Hydantoin is formed by a method entirely analogous to the formation of urea from ammonium cyanate, by intramolecular rearrangement. Glycocoll (glycin) is capable of forming salts with acids. The glycocoll isocyanate, obtained by mixing glycocoll sulphate and potassium cyanate, when heated rearranges into hydantoic acid.



The mother substance from which hydantoin is derived may be regarded as glyoxaline:

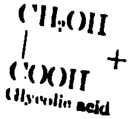


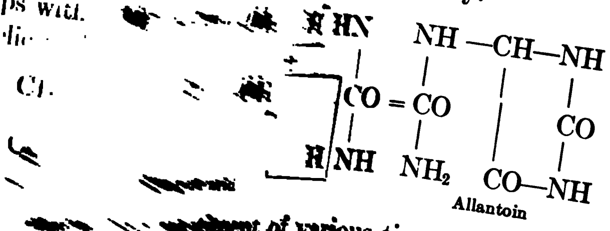
It is slightly soluble in co[illegible] [illegible]erred to as *imidaz*
153°. On heating with a [illegible] compound which me
acid, carbon dioxide, and [illegible] [illegible]stituted hydantoins
[illegible] acids other than gl
[illegible] amino acids are in som
[illegible] more favorable propertie
[illegible] and serve a useful pur
[illegible] substances.



[illegible] derivative of hydantoin. It

135. Glycoluri[illegible] of two molecules of urea
condensation of [illegible] glyoxylic acid (55), although
[illegible] an acid and an aldehyde,
[illegible] water and appears to act
[illegible] groups linked to one car-
[illegible] allantoin is one of the
This compo[illegible] this property.
groups with [illegible]
a cyclic [illegible]





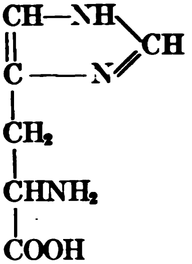
Allantoin

Ne[illegible] constituent of various tissues of animals,
ani[illegible] amounts. It is a constant constitu-
[illegible] of various animals, much more in other

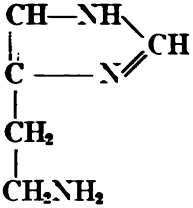
[illegible]s than in man. Allantoin is a crystalline compound having neither taste nor odor. Its solutions are neutral to litmus. It dissolves in 160 parts of cold water, but much more readily in hot water or hot alcohol. It melts with decomposition at 231°. It is precipitated by silver in ammoniacal solutions, but the precipitate is soluble in excess of ammonia. Lead, copper, and mercury likewise form insoluble compounds with it. It reduces Fehling's solution and is a disturbing factor in the employment of this reagent as a test for sugars in the urine.

On hydrolysis with acids or alkalies allantoin yields ammonia, carbon dioxide from the urea complexes, and acetic and oxalic acids. Its identification is effected by its isolation as the silver compound, which contains 40.73 % of silver and by a positive qualitative test for oxalic acid after hydrolysis of a sample.

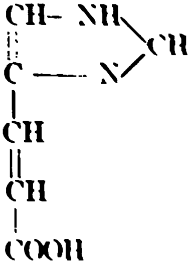
138. Histidine. — The glyoxaline or imidazol ring structure is present in one of the amino acids derived from the hydrolysis of many proteins, viz. *histidine:*



Histidine
(α-amino-β-imidazole-propionic acid)



Histamine
(β-imidazole-ethyl amine)



Urocanic acid
(β-imidazole-acrylic acid)

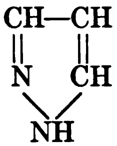
Histidine crystallizes in platelets which melt at 253° with decomposition. It dissolves readily in water, very slightly in alcohol, and not at all in ether. Its solution is alkaline to litmus. It forms salts with acids, the mono- and dihydrochlorides being of special importance in its isolation. It is precipitated from its solutions alkaline with sodium carbonate by mercuric chloride; by silver nitrate and ammonia or barium hydroxide; by mercuric sulphate in sulphuric acid solution; and by phosphotungstic acid.

Only l-histidine occurs in nature. It has a sweet taste. Putrefactive bacteria cause the elimination of carbon dioxide from it with the formation of *histamine*, or β-imidazolyl-ethylamine. While histidine itself is one of the essential amino acids which must be present in the food proteins, and can be introduced into the body without disturbance, histamine is a base which possesses most marked physiological action. Its action is primarily a stimulant effect on plain muscle. One part in 25 millions of Ringer's solution induces distinct contractions in a non-pregnant uterus. Larger doses induce tonic contraction.

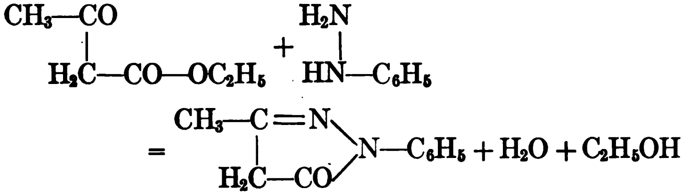
Histamine dihydrochloride, $C_5H_9N_3 . 2\,HCl$, is readily soluble in water, but sparingly in ethyl alcohol. It crystallizes in prisms which melt at 140°. The base forms a double salt with hydrochloro platinic acid which is soluble in hot water but very slightly soluble in alcohol. On boiling with bromine water histamine gives a claret color. It is precipitated by phosphotungstic acid, by ammoniacal silver solutions, and in alkaline solutions by mercuric chloride.

Urocanic acid or β-imidazole acrylic acid has been found in the urine of dogs, where it probably has its origin from histidine. It is not a normal constituent of the urine of the dog, but probably represents an abnormal type of metabolism.

Pyrazole,



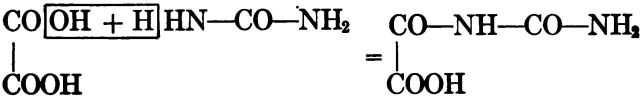
differs from imidazole in that the two nitrogen atoms in the ring are in position adjacent to each other. It is of importance in medicine because of its derivative, phenyl-dimethyl-pyrazolone, called antipyrine and phenazone. Methyl-phenyl-pyrazolone is formed by the action of phenyl hydrazine on aceto-acetic ester:



Antipyrine is formed in an analogous manner from methyl-phenyl-hydrazine.

Ureides of the Dibasic Acids

139. Oxaluric Acid and Parabanic. — Oxalic acid unites with urea with the separation of one molecule of water according to the following equation:



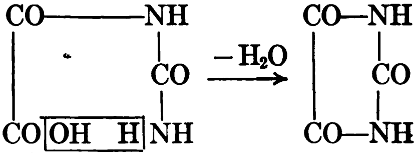
$$\begin{array}{l} CO\boxed{OH + H}HN{-}CO{-}NH_2 \\ | \\ COOH \end{array} = \begin{array}{l} CO{-}NH{-}CO{-}NH_2 \\ | \\ COOH \end{array}$$

Oxaluric acid

This type of compound is known as *acid ureide.*

It is not found practicable to stop the condensation of oxalic acid and urea at this stage. Oxaluric acid may be prepared by the careful hydrolysis of parabanic acid.

A second molecule of water may be separated with the formation of a cyclic compound:



Oxaluric acid
(Acid ureide)

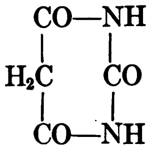
Parabanic acid

Parabanic acid is the simplest of the *ureides.*

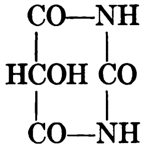
Oxaluric acid occurs in the urine in traces. It is a white crystalline compound soluble with difficulty in water. On warming with alkalies it is hydrolyzed to oxalic acid and urea.

Parabanic acid is likewise crystalline and is much more soluble than oxaluric acid. Parabanic acid is obtained by the oxidation of uric acid. Since its structure was understood from its synthesis from, and hydrolysis to, oxalic acid and urea it served to give a clue to the structure of the more complex uric acid molecule.

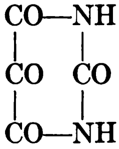
Ureides are also yielded by malonic, tartronic and mesoxalic acids. They are hydrolyzed to urea and the acids from which they were derived on boiling with acids or alkalies, the urea breaking down into ammonia and carbon dioxide. Their structures are illustrated by the following formulæ:



Barbituric acid
(Malonyl urea)

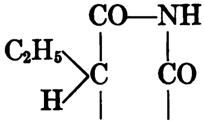


Dialuric acid
(Tartronyl urea)

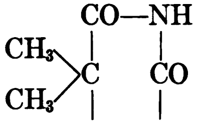


Alloxan
(Mesoxalyl urea)

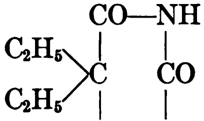
Malonyl urea is of special interest because of the narcotic effect of certain of its derivatives. The compound itself is without noticeable physiological action. Numerous derivatives have been prepared by substituting one or both hydrogen atoms of the malonyl group by alkyl and other groups. The following selected list will illustrate the remarkable influence which is exerted by certain groups as compared with others on the pharmacological action. Especially marked is the effect of accumulating alkyl groups, and the position occupied.



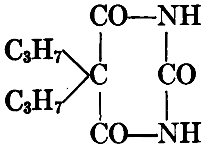
Monoethyl
malonyl urea
(1)



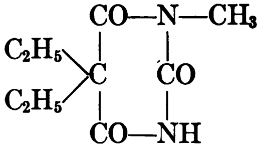
Dimethyl
malonyl urea
(2)



Diethyl
malonyl urea
(Veronal)
(3)



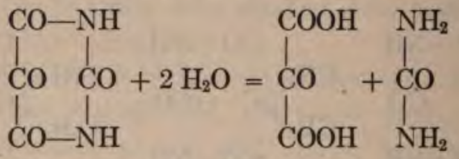
Dipropyl
malonyl urea
(4)



Diethyl-N-methyl
malonyl urea
(5)

When the derivatives (1) and (2) above were given to dogs weighing 6–8 kilograms, in doses of 3 to 4 grams, there was no noticeable effect. The diethyl derivative (3) in doses of 1–15 gm. induced deep sleep in about thirty minutes, lasting 24 hours. Of the dipropyl derivative (4) a 1-gram dose produced sleep after 30 minutes, lasting 48 hours, and 2 grams induced sleep within 15 minutes, and death. The toxic influence of introducing into diethyl barbituric acid (3) a methyl group linked to nitrogen as in (5) is very marked. A 1-gram dose induced sleep in 10 minutes which lasted two days and ended in death. Veronal and a few other similar compounds have found use as hypnotics.

140. Alloxan, or *mesoxalyl urea,* is formed from the oxidation of uric acid. On treatment with alkali it is hydrolyzed to mesoxalic acid and urea.

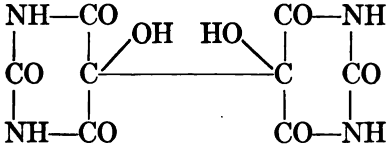


$$\begin{array}{ccccccc} \mathrm{CO} & - & \mathrm{NH} & & \mathrm{COOH} & & \mathrm{NH_2} \\ | & & | & & | & & | \\ \mathrm{CO} & & \mathrm{CO} & + 2\,\mathrm{H_2O} = & \mathrm{CO} & + & \mathrm{CO} \\ | & & | & & | & & | \\ \mathrm{CO} & - & \mathrm{NH} & & \mathrm{COOH} & & \mathrm{NH_2} \end{array}$$

On boiling alloxan with dilute nitric acid it is oxidized to parabanic acid and carbon dioxide. This is an example of the transformation of a six-membered ring to one containing but five (**113**).

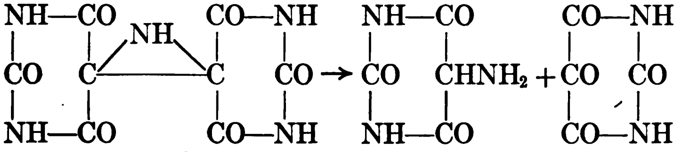
The formation of alloxan by the oxidation of uric acid served as further evidence as to the structure of a part of the molecule of that substance.

On reduction alloxan yields a derivative, alloxantine, containing two alcohol groups, which has double the molecular weight of alloxan itself. The structure assigned to it is the following.



Alloxantine

When alloxantine is treated with ammonia, it forms a salt-like derivative which is a purple-red dye called *murexide*. Murexide decomposes on hydrolysis into *uramil* and alloxan.

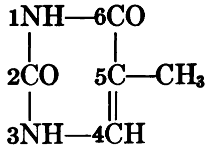


Murexide Uramil Alloxan

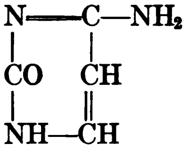
CHAPTER XIV

THE PYRIMIDINES, PYRAZINES AND PURINES

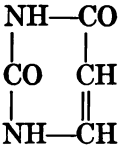
141. The Pyrimidines. In the nuclei of animal and plant cells occur the nucleic acids, complex compounds which on hydrolysis yield phosphoric acid, purines (**147**), pyrimidines, and a carbohydrate group (**163**). There have been found in nucleic acids three representatives of the pyrimidines:



2, 6-dioxy-5-methyl pyrimidine (Thymine)

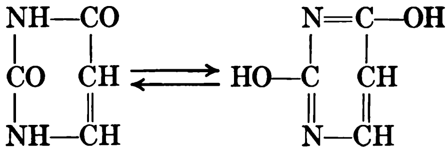


2-oxy-6-amino pyrimidine (Cytosine)

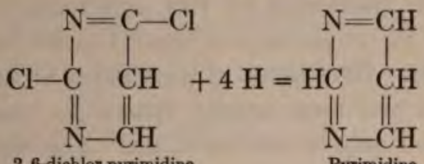


2, 6-dioxy pyrimidine (Uracil)

In the oxy pyrimidines there appears to be in the dissolved state a dynamic equilibrium between the molecules in which the oxygen is linked doubly to carbon, the *keto* form, with the enol form in which oxygen is singly linked to carbon and is in union with hydrogen forming a hydroxyl group:



When, *e.g.*, uracil is acted upon by phosphorus oxychloride, the oxygen atoms are not replaced by two chlorine atoms, but chlorine replaces hydroxyl, and 2,6-dichlor pyrimidine results. This can be reduced to pyrimidine itself.



2, 6-dichlor pyrimidine

Pyrimidine

Thymine and cytosine are obtained from animal nucleic acids, and uracil and cytosine from plant nucleic acids.

142. Thymine, $C_5H_6O_2N_2$, is difficultly soluble in cold, but readily in hot, water, and slightly soluble in alcohol. It is precipitated by silver nitrate in the presence of a slight excess of ammonium or barium hydroxide, the precipitate being soluble in an excess of the alkalies. It is likewise precipitated by mercuric chloride and nitrate in the presence of sodium hydroxide. Phosphotungstic acid does not precipitate it, but it is readily carried down where other substances are precipitated by this reagent. Thymine sinters when heated quickly, at 318°, and melts with the evolution of gas at 321°.

143. Cytosine, $C_4H_5ON_3H_2O$, is soluble in 129 parts of water at 25°. It crystallizes from hot water in prisms which decompose with gas evolution at 320°–325°. The salts formed with sulphuric or hydrochloric acids are readily soluble, those with picric acid and hydrochloroplatinic acid difficultly soluble in water.

Cytosine is precipitated by phosphotungstic acid (**147**), and by potassium bismuth iodide. It gives the Weidel reaction.

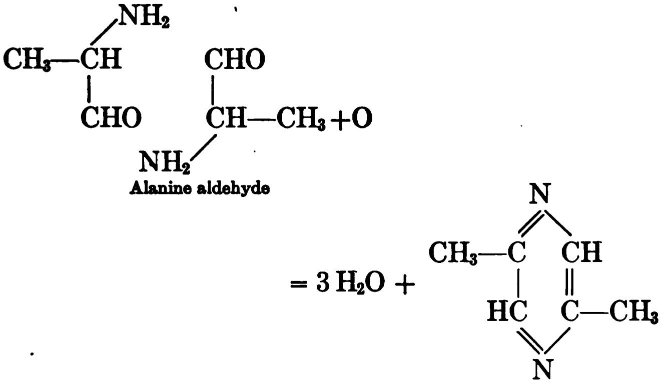
On treatment with nitrous acid it is converted into uracil. The mechanism of this transformation is the same as in the conversion of methyl amine into methyl alcohol (**46**). Here however there exists an equilibrium between the keto form usually written for uracil, and a small amount only of the enol form. The apparent replacement of the amino group by oxygen instead of by hydroxyl as in the primary amines is easily understood in the light of the behavior of urea and thiourea in the pseudo or iso form (**56, 58**) and of aceto acetic acid in the enol and keto forms (**127**).

144. Uracil, $C_4H_4O_2N_2$, is a white crystalline powder easily soluble in hot, difficultly soluble in cold, water. It dissolves readily in ammonia but scarcely at all in alcohol or ether. It is precipitated by mercuric nitrate, but not by phosphotungstic acid. It is precipitated under the same conditions as thymine by silver nitrate and ammonium or barium hydroxide. Uracil melts with decomposition at 335–338°. It likewise gives the Weidel reaction.

Numerous experiments in feeding animals with rations, all the constituents of which were known, have demonstrated that, although the nuclei of all cells yield at least two of the three pyrimidines just described, the diet need not contain any of these complexes. They can be synthesized in the animal body from certain of the amino acids yielded by the proteins of the food. The mode of formation of these compounds in the body is not understood.

PYRAZINE DERIVATIVES

145. Pyrazines. The paradiazines are represented by several products of biological interest. Amino aldehydes, on oxidation, can condense to form substituted pyrazines. Thus:

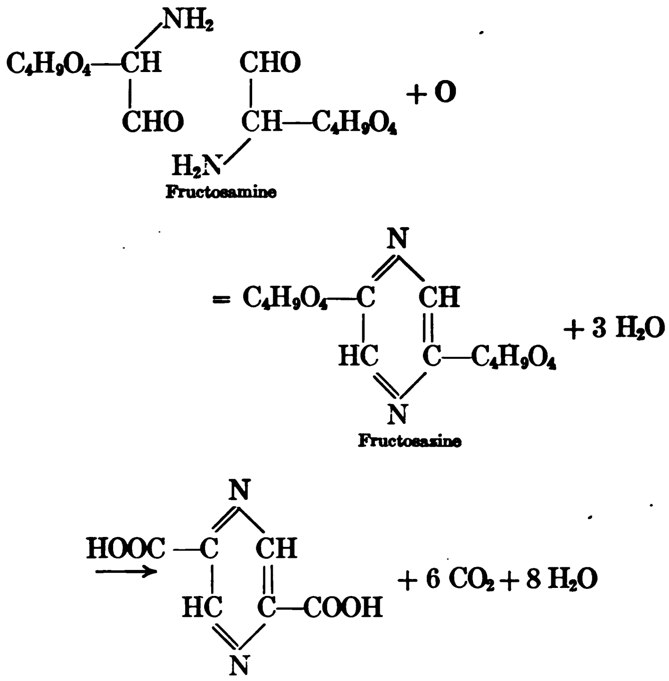


Alanine aldehyde

Dimethyl pyrazine

Amino acids are not attacked by reducing agents, but their esters can be reduced to amino aldehydes by means of sodium amalgam.

An instance of the occurrence of such a condensation in the animal body is the elimination in the urine of 2,5-pyrazine-dicarboxylic acid after injection of d-fructose, a ketone sugar (**156**), and glycocoll into the veins of a rabbit. The mechanism of the reaction is easily understood. Fructose is known to combine with ammonia to form fructosamine. This compound is an amino aldehyde which condenses to the pyrazine ring; thereafter the sugar complex is oxidized to the last carbon atom, which is converted into a carboxyl group:



Fructosamine

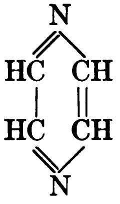
Fructosazine

2, 5-pyrazine dicarboxylic acid

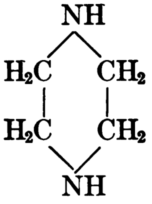
Fructosazine is oxidized outside the body by hydrogen peroxide with the formation of the same 2, 5-pyrazine dicarboxylic acid. The latter compound gives in neutral or faintly acid solution with ferrous sulphate a fine violet color which is easily seen in dilutions of 1 to 100,000 parts of water. By means of this reaction it has been shown that this pyrazine derivative when introduced into rabbits, even in small amounts, passes into the urine.

The above condensation is of interest because it points to the possibility of the reaction of carbohydrates in the body with certain intermediary decomposition products of the amino acids with the formation of heterocyclic compounds, *i.e.* cyclic compounds containing more than one kind of element in the ring.

146. Piperazine differs from pyrazine in that the double linkages are eliminated by the addition of hydrogen or substituting groups, *i.e.* it is a *reduced* pyrazine.

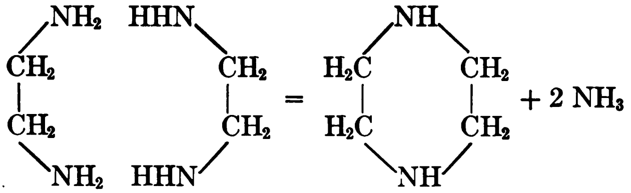


Pyrazine



Piperazine

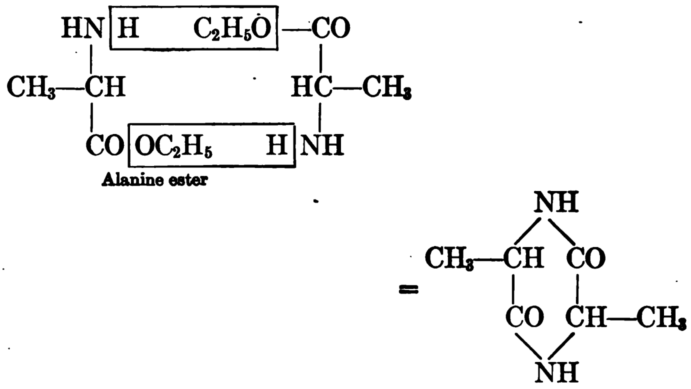
Piperazine is formed by heating the hydrochloric acid salt of ethylene diamine.



Ethylene diamine

Piperazine

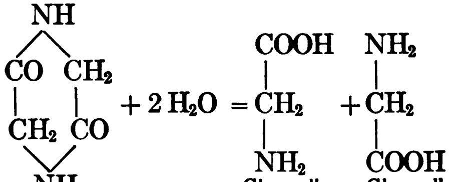
Esters of the amino acids change on standing, with the separation of alcohol, into their cyclic anhydrides, substituted ketone derivatives of piperazine. The change is accelerated by heating.



Alanine ester

2, 5-dimethyl-diketo piperazine

These cyclic anhydrides have in many cases much more favorable properties for manipulation, as sparing solubility, etc., than have the amino acids themselves. On heating with acids they are hydrolyzed to the free amino acids.



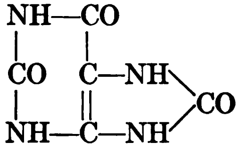
Diketo piperazine

Glycocoll

Glycocoll

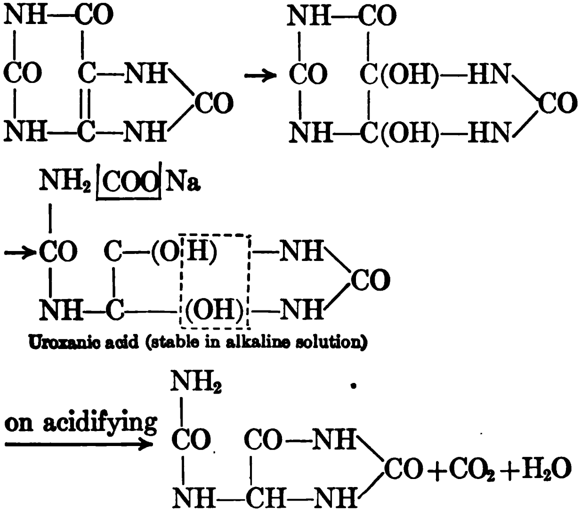
THE PURINES

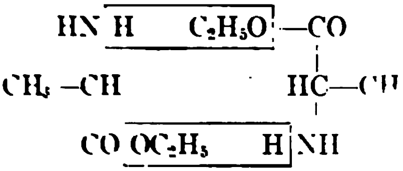
147. The researches of Emil Fischer on uric acid made clear the constitution of the group of compounds known as the purines. The constitution of uric acid was arrived at through the observation that on oxidation it yields *allantoin* (**137**). It contains therefore two urea groups in the molecule. The formation of parabanic acid and alloxan, whose structures are known from their formation from oxalic acid and urea, and mesoxalic acid and urea respectively, led to the proposal of the following structural formula:



Uric acid

The formation of allantoin from uric acid, which takes place on oxidation with potassium permanganate in sodium hydroxide solution, may be regarded as proceeding through the following stages:





Alanine ester

Fischer by

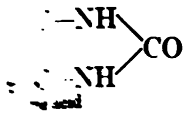
·H_3CNO

of uramil

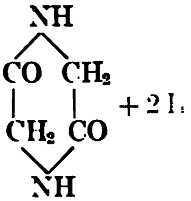
-NH—CO—NH₂

acid

H_2O



These cyclic anhydride
favorable properties for
bility, etc., than have
heating with acids they
acids.



Diketo piperazine

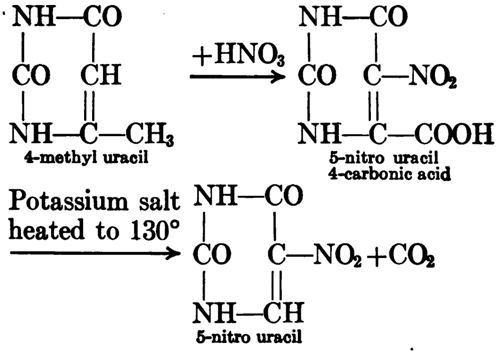
i reactions may be
...nium cyanate. It
...nge on heating, into
...he hydrogen atom is
...his is what happens.
...alic acid it loses a
...acid.

...al animals. Among
...of the total nitrogen
...ium urate. Mammals
...waste nitrogen as urea,
...d as purines and this

147. The research
clear the constitution
the purines. The co
through the obser

tly as uric acid and allantoin. Among mammals man occupies a peculiar position with respect to the excretion of uric acid. Studies of a considerable number of animals of diverse types have shown that the greater part of the purine nitrogen is eliminated in the form of allantoin. In man there is but a trace of allantoin excreted, practically all of the purine nitrogen appearing in the urine as uric acid. This finds its explanation in the fact that the reaction by which uric acid is transformed into allantoin, oxidation and hydrolysis, is catalyzed by a specific enzyme. This enzyme, which can be recognized in a tissue by its ability, under suitably regulated conditions, to destroy uric acid, is present in the tissues of all animals except man. In the absence of this catalytic agent the conversion of uric acid to allantoin goes on with extreme slowness.

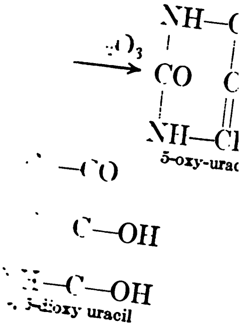
Uric acid has been synthesized by a considerable number of methods starting from widely different materials. The early synthesis (1888) by Behrend and Roosen, which is particularly instructive, is illustrated by the following reactions:

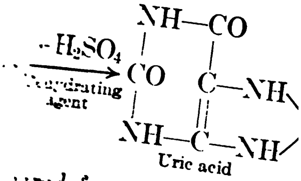


4-methyl uracil

5-nitro uracil 4-carbonic acid

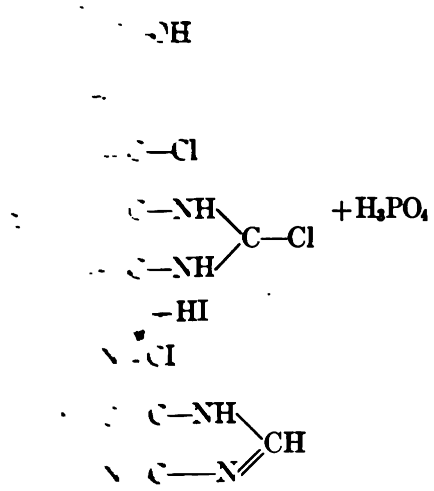
5-nitro uracil





ated from urine. It ex
sodium and potassium sa
gram of dipotassiu
water at room temperatu
in 77 c.c. The free ur
parts of water at room tem
ric acid to urine, to
crystallizes out usually
pigmented. By dissolv-
c.) and diluting with
and may thus be purified.
acid, forming two series of
The ammonium, calcium,
soluble than are those

[illegible] purine, which results [illegible] phosphorus oxychloride on



[illegible] purine

u [illegible]

ai [illegible]

aci [illegible] these reactions as if they

per [illegible]

disti [illegible] which melts at 211–

arran [illegible] and forms salts with various

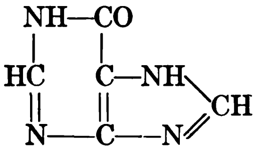
ing in [illegible]

water t [illegible] There are besides uric acid

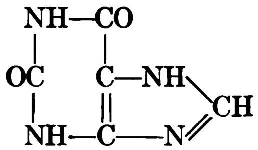
Uric ac [illegible] great biological interest,

salts, acid [illegible] Their relation to uric

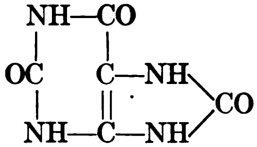
and barium [illegible]



6-oxy purine (Hypoxanthine)



2, 6-dioxy purine (Xanthine)



2, 6, 8-trioxy purine (Uric acid)

Hypoxanthine is a crystalline compound soluble in 69.5 parts of boiling water and in 1400 parts at 19°. It dissolves readily in mineral acids and alkalies. It is insoluble in alcohol. The hydrochloride, $C_5H_4N_4O.HCl + H_2O$, is decomposed on crystallization from water, but can be crystallized from concentrated hydrochloric acid. The sulphate and nitrate are likewise decomposed by water. Hypoxanthine picrate is a characteristic salt. Hypoxanthine is precipitated from its solutions by ammoniacal silver nitrate.

Hypoxanthine is found in the muscles and organs of the animal body and is accumulated in beef extract. It is likewise widely distributed in plants.

Xanthine, $C_5H_4N_4O_2$, is likewise found in animal tissues and widely distributed in plants. It is very slightly soluble in water, about 1 to 14,000 parts at 16°, and in 1400 parts of boiling water. It dissolves more readily in alkalies. Xanthine, like hypoxanthine, forms salts with acids. However, it also forms crystalline compounds with alkalies.

On evaporation [illegible] a *guanase* which cata-
remains a yellow [illegible] into xanthine as de-
hydroxide [illegible] tain all the enzymes
red. This is a [illegible] of the amino purines
[illegible] not found in the tissues
[illegible] m the spleen and liver

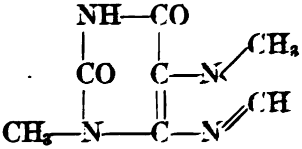
148. Adenine [illegible] spleen, but is present in
purine found [illegible] which accelerates the
It is a [illegible] xanthine is called *hypo-*
plant and [illegible] oxidizes xanthine to uric
at 360-365° [illegible] ase. The enzyme which
It forms [illegible] of uric acid to allantoin is
of hypo [illegible] is employed to designate
water. [illegible]
The latter [illegible] animal and plant origin con-
Adenine [illegible] and guanine. The hypo-
It is [illegible] acid found in the tissues are
Adenine [illegible] and oxidation of these.
purine [illegible] ing experiments with young
[illegible] h diets entirely free from
[illegible] and hence the synthesis of
[illegible] at the normal rate. Such
[illegible] acid. There is no doubt
[illegible] animals adenine and guanine
[illegible] The substances from which
[illegible] are not known with cer-
[illegible] with birds make it highly prob-
[illegible] ammonia, and lactic acid. In
[illegible] of uric acid is the liver. When
[illegible] the bird has been found to

excrete, during the few hours it can live, ammonia and lactic acid instead of uric acid.

THE METHYL PURINES

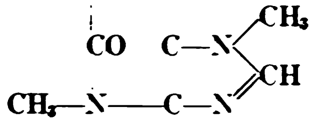
149. Aside from the purines ingested as adenine and guanine or their degradation products there occur in plant foods two important methylated purines, theobromine and caffeine.

Theobromine *is* 2,6-*dioxy*-3,7-*dimethyl purine*:



Occurs in the cocoa bean, and is found in chocolate to the extent of 1 to 2 per cent. It is a dimethyl xanthine. It is a white crystalline powder, soluble in ether, insoluble in alcohol and water, but somewhat soluble in hot chloroform. It forms crystalline salts with strong acids, but these are decomposed into the base and acid by water. It sublimes unchanged at 290°. It is a powerful diuretic and nerve stimulant. It has a bitter taste. The hydrochloride and salicylate are also much employed.

Caffeine *is* 2,6-*dioxy*-1,3,7-*trimethyl purine*:



It occurs in tea and coffee, guarana, and in kola nuts. Coffee contains about one per cent. It is soluble in 80 parts of water; 55 parts of alcohol, 7 parts of chloroform, and 555 parts of ether at 15°. Caffeine crystallizes from water in white fleecy masses of silky needles, having a bitter taste. It sublimes at 178°.

Caffeine is a diuretic and cerebral stimulant and has a pronounced stimulating action on the heart.

In passing through the body caffeine and theobromine are partially demethylated, and they appear in the urine to some extent as monomethyl and dimethyl purines. In part the methyl groups are completely removed, the nucleus being excreted as uric acid.

CHAPTER XV

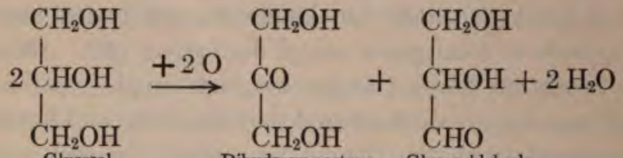
THE CARBOHYDRATES

150. There is found in nature a large group of compounds to which the general name *carbohydrates* is applied. These are either aldehyde alcohols or ketone alcohols, or are converted into aldehyde alcohols or ketone alcohols on hydrolysis. The carbohydrates include the sugars, starches, celluloses, gums, pectins, etc. In many of them the composition corresponds closely to the general formula $C_n(H_2O)_n$, or one molecule of water to each carbon atom. Thus, cane and beet sugar have the formula $C_{12}H_{22}O_{11}$ which corresponds to $C_{12}\,11(H_2O)$; glucose and fructose, $C_6H_{12}O_6 = C_6\,6(H_2O)$; starch, the molecule of which is very large, corresponds to the formula $C_6\,5(H_2O)$. It was from this relationship that they received the name carbohydrate. There are several representatives of the carbohydrates which do not conform to this formula; and there are on the other hand a number of compounds totally unrelated chemically to the carbohydrates which contain carbon, hydrogen, and oxygen, the two latter elements in the proportion to form water. As examples may be cited formaldehyde, CH_2O, acetic acid, $C_2H_4O_2$, and lactic acid, $C_3H_6O_3$. The carbohydrates are of the greatest importance as a source of energy to the animal body, and as a rule among the herbivora and omnivora they constitute more than one hydroxyl is untenable. Each one except the end ones must be linked on two sides to carbon and on one to hydroxyl. The remaining bond must be occupied by hydrogen. By such reasoning we arrive at the conclusion that the structure of the aldohexoses is the following:

$$CH_2OH—CHOH—CHOH—CHOH—CHOH—CHO$$

Monosaccharide

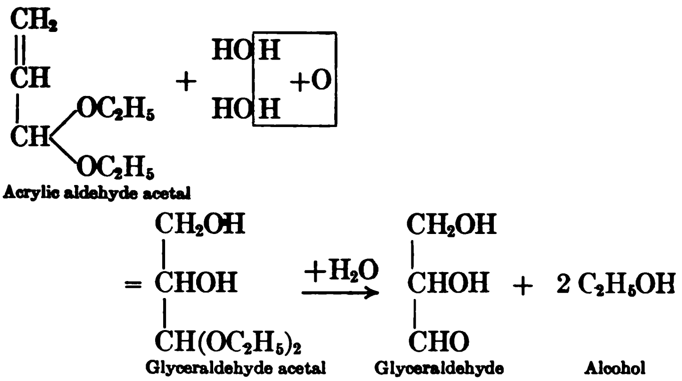
151. Methods of Synthesis of the Monoses. — 1. By the carefully regulated oxidation of the polyatomic alcohols. As an example may serve the oxidation of glycerol. It has previously been described (**36**) how by cautious oxidation of this triatomic alcohol there results glyceraldehyde, which in the terminology of the carbohydrates is glycerose. The chief product of this reaction is always the isomer dihydroxy acetone:



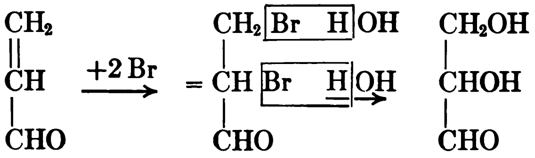
$$2\begin{array}{l}CH_2OH\\|\\CHOH\\|\\CH_2OH\end{array} \xrightarrow{+2\,O} \begin{array}{l}CH_2OH\\|\\CO\\|\\CH_2OH\end{array} + \begin{array}{l}CH_2OH\\|\\CHOH\\|\\CHO\end{array} + 2\,H_2O$$

Glycerol Dihydroxy acetone Glyceraldehyde

Glyceraldehyde can be prepared free from dihydroxy acetone by the oxidation of acrolein (**86**), the aldehyde group of the latter being protected during the process by first converting it into the acetal (**32**). As in the case of the fatty acids, oxidation of compounds containing doubly linked carbon leads first to the formation of hydroxy groups at this point.



2. By hydrolysis of brom aldehydes with barium hydroxide. Mention has aleady been made of the formation of glycol aldehyde from brom acetaldehyde by this method (**35**). By this method glyceraldehyde may also be prepared. Starting with acrylic aldehyde, two bromine atoms are added. The dibrom propyl aldehyde reacts with water when heated with barium hydroxide, the bromine atoms being replaced by hydroxyl.



3. When formaldehyde is treated with weak alkali (limewater) it condenses to a mixture of compounds of the formula $C_6H_{12}O_6$. The mixture is sirup-like and sweet. It has received the name *formose*. In its formation six molecules of formaldehyde condense to form a mixture of aldohexoses:

inize adenine to hypoxanthine, and a *guanase* which catalyzes the transformation of guanine into xanthine as described above. Not all tissues contain all the enzymes necessary to the transformation of the amino purines into oxypurines. Thus adenase is not found in the tissues of the rat. Guanase is absent from the spleen and liver of the pig and from the human spleen, but is present in most other tissues. The enzyme which accelerates the oxidation of hypoxanthine into xanthine is called *hypoxanthine-oxidase*; that which oxidizes xanthine to uric acid is called xanthine-oxidase. The enzyme which accelerates the oxidation of uric acid to allantoin is called *uricase*. The ending *ase* is employed to designate enzymes or organic catalysers.

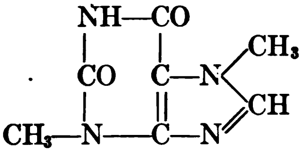
The nucleic acids of both animal and plant origin contain but two purines, adenine and guanine. The hypoxanthine, xanthine, and uric acid found in the tissues are formed by the deamination and oxidation of these.

Within recent years feeding experiments with young animals have shown that with diets entirely free from any of the purines, growth and hence the synthesis of nucleic acids can take place at the normal rate. Such animals regularly excrete uric acid. There is no doubt that in such experimental animals adenine and guanine are produced synthetically. The substances from which purines are formed in mammals are not known with certainty, but experiments with birds make it highly probable that they are urea, ammonia, and lactic acid. In birds the seat of synthesis of uric acid is the liver. When the liver of a bird is excised the bird has been found to excrete, during the few hours it can live, ammonia and lactic acid instead of uric acid.

THE METHYL PURINES

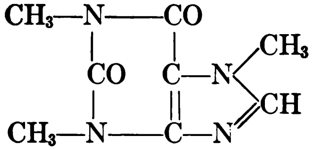
149. Aside from the purines ingested as adenine and guanine or their degradation products there occur in plant foods two important methylated purines, theobromine and caffeine.

Theobromine *is* 2,6-*dioxy*-3,7-*dimethyl purine*:



Occurs in the cocoa bean, and is found in chocolate to the extent of 1 to 2 per cent. It is a dimethyl xanthine. It is a white crystalline powder, soluble in ether, insoluble in alcohol and water, but somewhat soluble in hot chloroform. It forms crystalline salts with strong acids, but these are decomposed into the base and acid by water. It sublimes unchanged at 290°. It is a powerful diuretic and nerve stimulant. It has a bitter taste. The hydrochloride and salicylate are also much employed.

Caffeine *is* 2,6-*dioxy*-1,3,7-*trimethyl purine*:



(aldehyde or ketone group) at least one *carbinol group* $\mathrm{H\overset{|}{\underset{|}{C}}OH}$, it must follow that for each of the aldoses, there are two acids which can be derived by oxidation and an alcohol which can be obtained by reduction. The following résumé of the simple aldoses, together with the corresponding alcohols and acids, will serve to illustrate their relationships:

Diose, $C_2H_4O_2$

$$\begin{array}{cccc}
\mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{COOH} \\
| & | & | & | \\
\mathrm{CH_2OH} & \mathrm{CHO} & \mathrm{COOH} & \mathrm{COOH} \\
\text{Glycol} & \text{Glycol aldehyde} & \text{Glycolic acid} & \text{Oxalic acid}
\end{array}$$

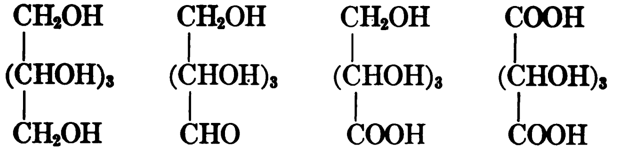
Triose (glycerose), $C_3H_6O_3$

$$\begin{array}{cccc}
\mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{COOH} \\
| & | & | & | \\
\mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} \\
| & | & | & | \\
\mathrm{CH_2OH} & \mathrm{CHO} & \mathrm{COOH} & \mathrm{COOH} \\
\text{Glycerol} & \text{Glycerose} & \text{Glyceric acid} & \text{Tartronic acid}
\end{array}$$

Tetrose (erythrose), $C_4H_8O_4$

$$\begin{array}{cccc}
\mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{CH_2OH} & \mathrm{COOH} \\
| & | & | & | \\
\mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} \\
| & | & | & | \\
\mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} & \mathrm{CHOH} \\
| & | & | & | \\
\mathrm{CH_2OH} & \mathrm{CHO} & \mathrm{COOH} & \mathrm{COOH} \\
\text{Erythrite} & \text{Erythrose} & \text{Erythronic acid} & \text{Tartaric acid} \\
 & & \text{(Trioxybutyric acid)} &
\end{array}$$

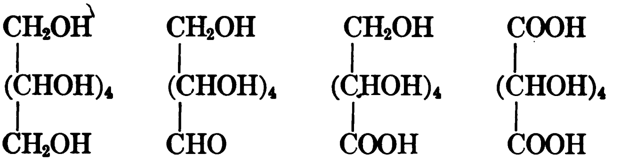
Pentose (xylose, arabinose, etc.)



$$\begin{array}{c} CH_2OH \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} \qquad \begin{array}{c} CH_2OH \\ | \\ (CHOH)_3 \\ | \\ CHO \end{array} \qquad \begin{array}{c} CH_2OH \\ | \\ (CHOH)_3 \\ | \\ COOH \end{array} \qquad \begin{array}{c} COOH \\ | \\ (CHOH)_3 \\ | \\ COOH \end{array}$$

Pentite Pentose Pentonic acid Trioxyglutaric acid

Hexose (glucose, mannose, galactose, etc.)

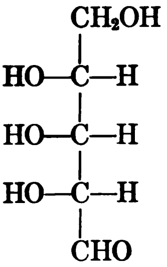


$$\begin{array}{c} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \end{array} \qquad \begin{array}{c} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CHO \end{array} \qquad \begin{array}{c} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ COOH \end{array} \qquad \begin{array}{c} COOH \\ | \\ (CHOH)_4 \\ | \\ COOH \end{array}$$

Hexite Hexose Hexonic acid Tetraoxyadipic acid

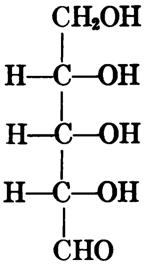
Glycol has no carbon atom possessing asymmetry and therefore shows no optical activity. All the other aldoses possess one or more asymmetric carbon atoms and therefore exist in two or more isomeric forms. Glycolaldehyde is an unstable substance and has never been isolated from plant or animal tissues. The same is true of glyceraldehyde. Both of these are known through the synthetic products only.

A tetrite, inactive erythrite (i-erythrite) is found free in the Alga, *Protococcus vulgaris*. Tetroses have never been found in nature, but have been prepared synthetically. There are theoretically possible twelve isomeric aldopentoses, viz., an optically inactive, a dextro- and a levorotatory form of each of the four possible aldopentoses, whose formulæ are illustrated as follows:



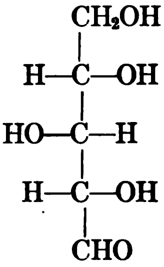
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(1) l-ribose



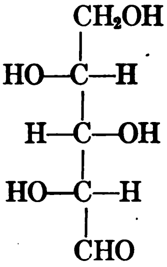
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(2) d-ribose



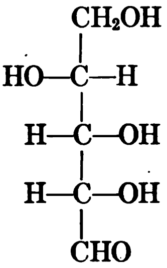
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(3) l-xylose



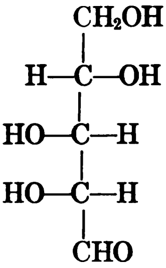
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(4) d-xylose



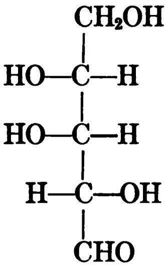
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(5) l-lyxose



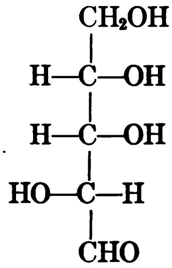
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

(6) d-lyxose



$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

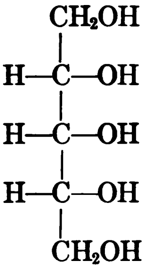
(7) l-arabinose



$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CHO} & \end{array}$$

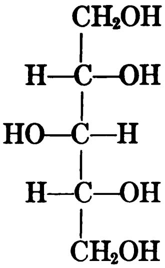
(8) d-arabinose

From these are obtained on reducing the aldehyde groups to primary alcohol radicals, the following alcohols, the pentites.



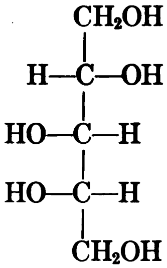
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

Adonite
(From l- and d-ribose)



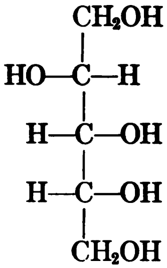
$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

Xylite
(From l- and d-xylose)



$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

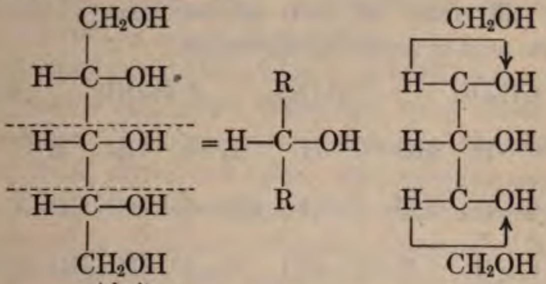
l-arabite
(From l-lyxose and l-arabinose)



$$\begin{array}{rcl} & \mathrm{CH_2OH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

d-arabite
(From d-lyxose and d-arabinose)

Adonite and xylite are optically inactive although each contains two asymmetric carbon atoms. The central carbon atom in the pentose loses its asymmetry when the carbonyl group is changed to carbinol, for in the case of adonite the two groups marked off by the dotted lines are alike and there exists accordingly the same type of *internal compensation* with respect to influence on light, as was seen in mesotartaric acid (**123**).

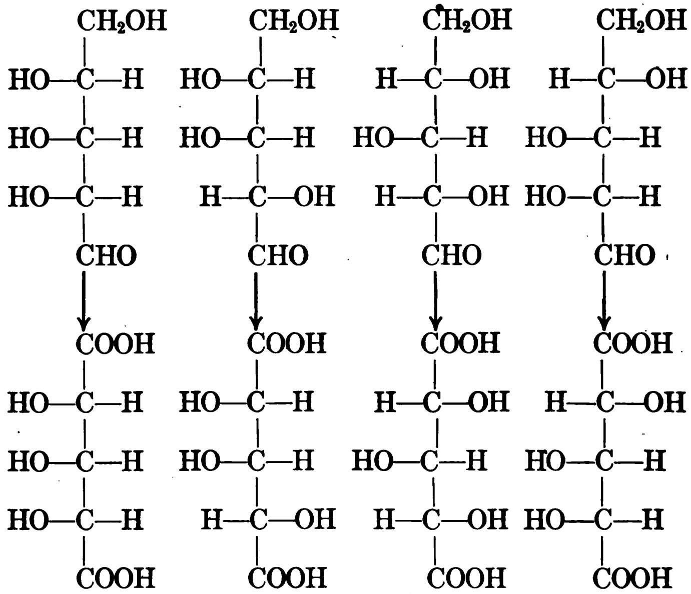


Adonite

When the symmetry of the molecule is destroyed by oxidation of one primary alcohol radical, the central carbon atom again becomes asymmetric and optical activity is restored. A simple test as to whether a compound is inactive because of intramolecular compensation, is to determine whether by rotating the projection formula 180° *in the plane of the paper* it can be made to coincide with the projection formula of its mirror image. Whenever the two formulæ can be made to coincide, the molecules which they represent are identical and therefore cannot be optically different. l-arabinose and l-xylose and possibly d-ribose occur in nature, while lyxose does not.

152. Determination of Structure. — We may now inquire in what way it is possible to decide which of the several formulæ (1–8) of the aldopentoses is to be assigned to each of the naturally occurring sugars. If the projection formula for each one of the four pentoses having different configuration can be determined, the other four, being their mirror images, can at once be properly named.

If the four forms in question (page 296) be oxidized at both the aldehyde group and at the primary alcohol group there will result for each pentose form a trihydroxy glutaric acid of similar configuration.



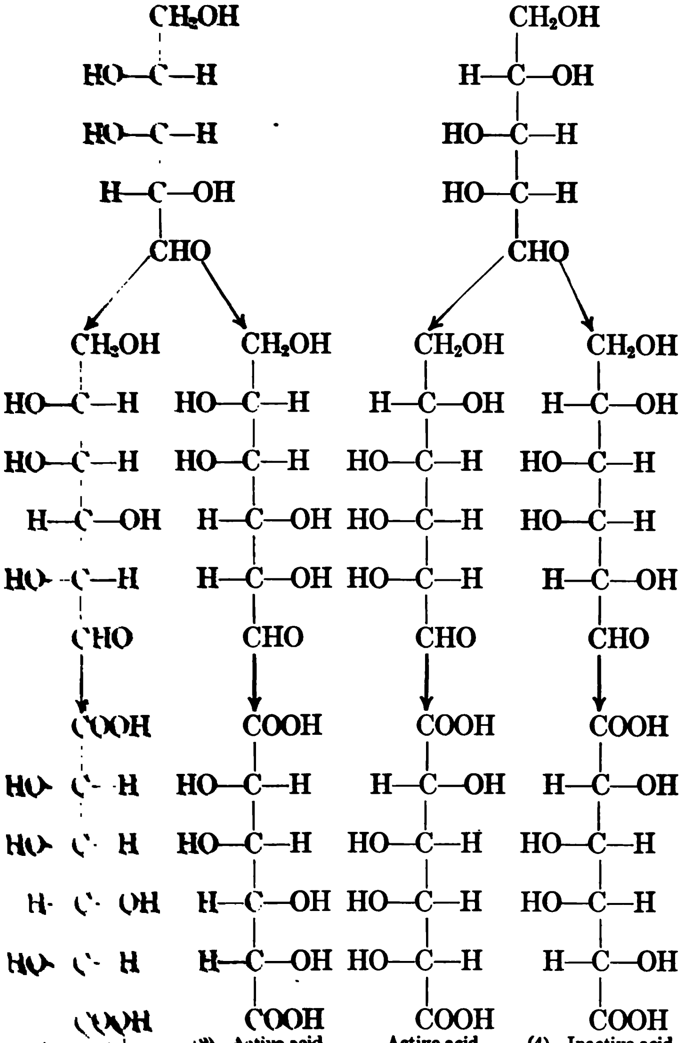
(1) Inactive (2) Active (3) Inactive (4) Active

Two of these will be active and two inactive because on converting both end carbon atoms into similar groups (carboxyl), the central carbon atom in (1) and (3) loses its asymmetry and the molecule presents internal optical compensation (**151**).

Arabinose and ribose yield the same osazone, so their difference in configuration must lie in the H and OH on the carbon atom next to the aldehyde group, since these only are displaced in osazone formation (p. 285). The pairs of formulæ which fulfill this condition are (1) and (2) or (3) and (4) (p. 298). Arabinose and ribose must be represented by one of these pairs.

Arabinose on oxidation yields an optically active trihydroxy glutaric acid, while ribose and xylose produce inactive acids. This necessitates assigning the formulæ (1) or (3) to ribose and xylose, and arabinose must be either (2) or (4). Lyxose must then be whichever of the formulæ (2) or (4) is not assigned to arabinose. But the fact that arabinose and ribose yield the same osazone shows that if arabinose is (2) ribose must be (1), or if arabinose is (4) ribose must be (3).

When a pentose is subjected to Kiliani's reaction (p. 290) the resulting hexose will present two different configurations, since when the hydroxyl group is formed in the cyanhydrin formation there is just as great a chance that it will take up its position on one side as another (see lactic acid, **66**). When the hexoses derived from arabinose or xylose are oxidized to dibasic acids, both are found to be active, while those derived from lyxose are one active and the other inactive. The formulas for inactive acids must show internal compensation, since each contains two asymmetric carbon atoms.

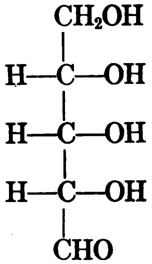


Active acid (2) Active acid Active acid (4) Inactive acid

It follows, therefore, that the formula of arabinose must be (2), and ribose which yields the same osazone must be (1), and lyxose, being the only pentose from which hexoses are derived yielding an active and an inactive dicarboxylic acid, must be (4). Xylose must then be represented by (3), the only one remaining.

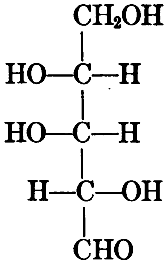
THE PENTOSES

153. The structural formulæ for the three biologically important pentoses are the following:



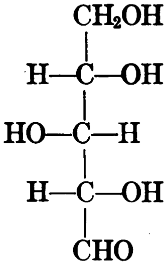
$$\begin{array}{c} CH_2OH \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CHO \end{array}$$

d-ribose



$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ CHO \end{array}$$

l-arabinose



$$\begin{array}{c} CH_2OH \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ CHO \end{array}$$

l-xylose

d-ribose has been found only in the nucleic acids. Judging from the amount of furfural obtained from various tissues when these are distilled with acids, the human body contains about 10.5 grams of pentose. l-arabinose and l-xylose are apparently not found in nature in the free state, but only in the form of their polysaccharides, araban and xylan (**162**) in the gums and woody tissues of plants. The pentoses are water-soluble and show the general properties of alcohols and aldehydes. l-arabinose is obtained from the hydrolysis of gum arabic, peach gum, cherry gum, etc. It crystallizes in prisms and has a sweet

designation l-arabinose
relationship to glucose

rolysis of xylan, which is
in the straw of wheat,
It crystallizes in doubly
at 144–145°.
more common hexoses, the
xidation in the animal body
After the administration
they appear in the urine.
dividuals, there is excreted regu-
of the character of the diet, a
entose which has not been iden-
probably arabinose or ribose.
has been reported in the
chronic *pentosuria* appears
is apparently hereditary.
equently follows the ingestion
of which contain pentoses or

The reaction for the estima-
polysaccharides depends upon
ural on treatment with mineral
is distilled off with steam
loroglucinol (**194**). The latter
mpound with which furfural forms
compound on condensation. From the
phloroglucide the pentose content of the
mined. Thiobarbituric acid (**139**) by virtue

of its hydroxyl group likewise condenses with furfural to form a very insoluble product, which has been made the basis of a quantitative estimation of the pentoses.

With certain other cyclic polyalcohols the pentoses in acid solution give characteristic color reactions. Most important is the colored derivative with *orcin* (**196**).

154. Methyl Pentoses. — There is found in nature a class of compounds called *glucosides* (**161**) which contain a hexose, a disaccharide, or a methyl pentose in union with some other substance. The second substances vary greatly in their chemical character, but in most instances they are alcohols. They are found in seeds, roots, leaves and bark of plants, and are broken up by acids or by specific enzymes, but not by alkalies, into their constitutents. Among these glucosides quercitrin, xanthorhamnin and certain of the saponins (**161**) yield the methyl pentose *rhamnose.* This sugar is still occasionally referred to as isodulcite, a name which it once held owing to the mistaken belief that it was a hexahydric alcohol. Its formula is

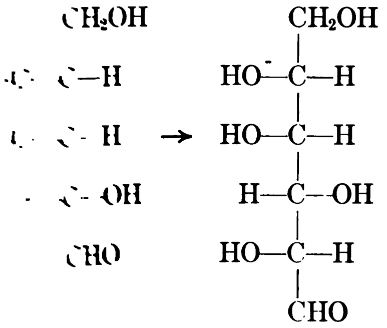
$$CH_3{-}CHOH{-}CHOH{-}CHOH{-}CHOH{-}CHO$$

Rhamnose is crystalline, the crystals containing one molecule of water. It melts at 93°.

Other methyl pentoses found in nature are *fucose* in the form of the polysaccharide fucosan in certain seaweeds, and *chinovose* in the form of the glucoside chinovin found especially in cinchona bark.

155. The Hexoses. — There are sixteen possible stereochemical isomers of the sugars having the formula

These represent eight forms
of the eight pairs of sugars
known, so that but six need be
ural formulæ are arrived at
e pentoses and the optical prop-
which they yield on oxidation.
151) is applied to arabinose,
ucing the resulting lactone two
very common in nature, viz.,
has been pointed out in describ-
exoses from pentoses that the only
be due to the difference in position
n the carbon atom adjoining the
ose and mannose must be repre-
two structures, A and B: —

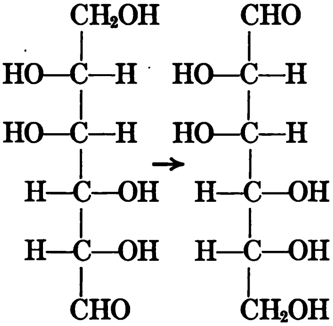


$$\begin{array}{c} CH_2OH \\ C-H \\ C-H \\ C-OH \\ CHO \end{array} \rightarrow \begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ CHO \end{array}$$

arabinose B

ized, it yields a dibasic acid called
One of the hexoses not found in
by Fischer by synthesis, viz. gulose,
ation saccharic acid. This being the

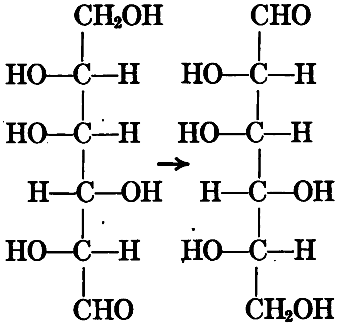
case, the arrangement of the H and OH groups on all the four central carbon atoms must be alike in glucose and gulose, for these carbon atoms and their H and OH groups are not affected in any way by transforming the sugar into saccharic acid. It follows that the difference between glucose and gulose must be explainable as the result of the asymmetry due to the difference in position of the aldehyde and primary alcohol groups with respect to the peculiar arrangement of the rest of the molecule. It also follows that any formula which is the *same* when the CHO and CH_2OH groups are transposed cannot represent glucose and gulose, for such a formula could not represent two different sugars. In the following formulæ C fulfills the last condition, while D, on transposing the end groups, leads to a different sugar.



$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CHO \end{array} \rightarrow \begin{array}{c} CHO \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CH_2OH \end{array}$$

C

Same sugar after transposing terminal groups

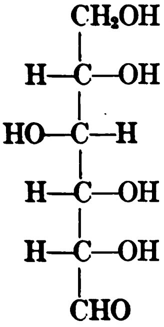


$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ CHO \end{array} \rightarrow \begin{array}{c} CHO \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ CH_2OH \end{array}$$

D

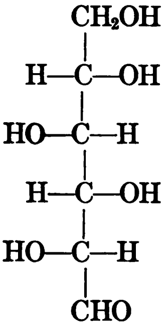
Different sugar after transposing terminal groups

Glucose is therefore represented by the formula D and mannose is C. The formula F must accordingly represent gulose.



$$\begin{array}{c} CH_2OH \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ CHO \end{array}$$

F

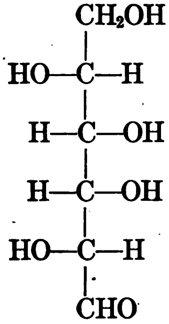


$$\begin{array}{c} CH_2OH \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ CHO \end{array}$$

G

Idose, another sugar not found in nature but obtained synthetically, yields the same osazone as gulose, and their difference in structure rests therefore in the positions of the H and OH adjacent to the aldehyde group, since only these two are affected in osazone formation. This is further supported by the fact that xylose when subjected to Kiliani's reaction yields a mixture of gulose and idose. It has been already shown that gulose is represented by F, so idose must have the structure G.

d-galactose is a naturally occurring sugar. On reduction it yields an inactive hexahydric alcohol and on oxidation an inactive dibasic acid. When converted by Kiliani's reaction into two heptonic acids and on further oxidation of the latter into pentahydroxy pimelic acids, both products are optically active. From considerations analogous to those described in arriving at the structures of other hexoses, the formula ascribed to galactose is the following:



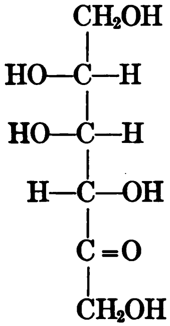
$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ H-C-OH \\ | \\ HO-C-H \\ | \\ CHO \end{array}$$

156. The Ketoses. — There are found in nature but two representatives of the ketohexoses, viz. fructose and sorbose. The latter is very rare, but the former is one of the very widespread and important sugars.

d-fructose is found together with glucose in sweet fruits and is chemically combined with it in cane sugar, with glucose and galactose in raffinose, a trisaccharide found in cotton seed, with mannose as mannotetrose found in manna, and with galactose in lupeose, a tetrose found in the seeds of the lupine. There is a starch-like polysaccharide, inulin, in the tubers of the dahlia, which yields fructose on hydrolysis.

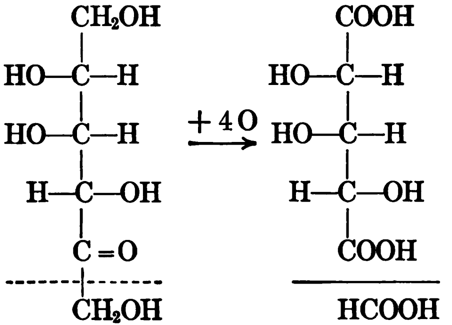
d-fructose is found in nature. It is levorotatory, notwithstanding its designation as d-fructose. Fischer designated as the d-, l-, or i- form all monoses which are derived from a d-, l-, or i-hexose respectively. d-fructose can be derived from d-glucose, hence its name. The letter denoting the form of a monose signifies to what optical form of hexose the monose is related, and not the direction of its rotation of the plane of polarized light.

It is distinctly sweeter than any other sugar, and is more unstable than the aldohexoses. The constitution assigned to it is:



$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ C=O \\ | \\ CH_2OH \end{array}$$

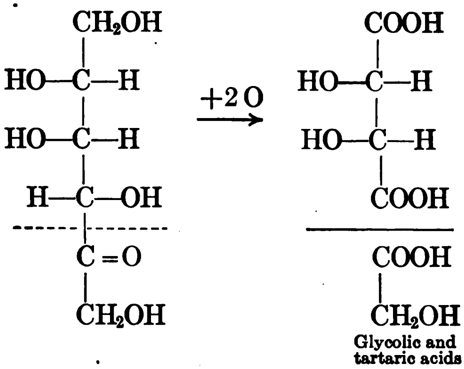
On oxidation it yields formic, glycolic, tartaric, and trihydroxy glutaric acids.



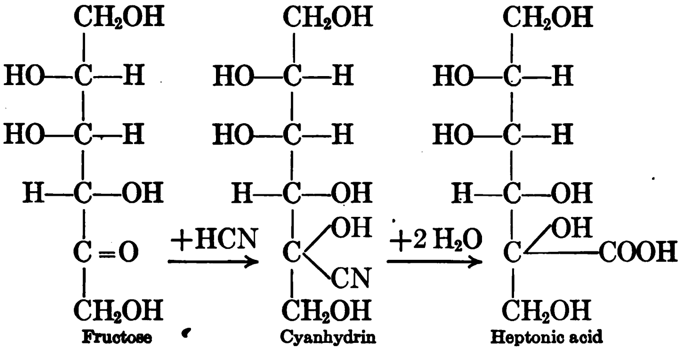
$$\begin{array}{c} CH_2OH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ C=O \\ \text{-------}|\text{-------} \\ CH_2OH \end{array} \xrightarrow{+4O} \begin{array}{c} COOH \\ | \\ HO-C-H \\ | \\ HO-C-H \\ | \\ H-C-OH \\ | \\ COOH \\ \hline HCOOH \end{array}$$

Trihydroxy glutaric and formic acids

Since the cleavage may take place on one side of the carbonyl group as well as on the other, this group of oxidation products shows that the carbonyl group is but one removed from the terminal carbon atom.

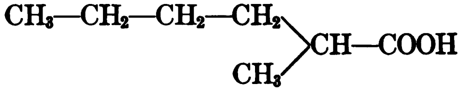


Whereas the aldopentoses and aldohexoses yield normal carbon chain derivatives when subjected to the cyanhydrin synthesis (page 287), fructose yields an acid with the following structure:



This harmonizes with the assumption that the structure assigned to fructose is correct, for the ketone structure of fructose must necessarily lead to the formation of a branched carbon chain.

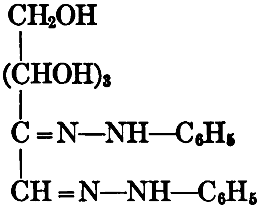
This heptonic acid when reduced by heating with hydriodic acid (**149**) is changed into methyl-*n*-butyl acetic acid



$$\begin{array}{l} CH_3{-}CH_2{-}CH_2{-}CH_2\diagdown \\ \qquad\qquad\qquad\qquad\qquad\quad CH{-}COOH \\ \qquad\qquad\qquad\quad\;\; CH_3\diagup \end{array}$$

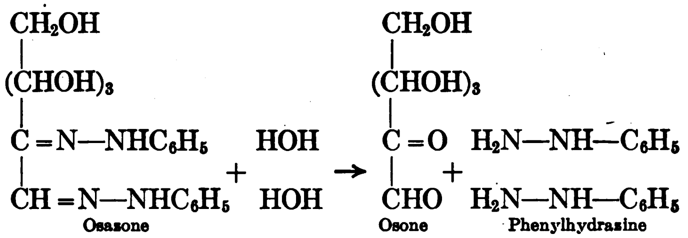
which has been synthesized by the Claisen reaction (**127**).

The same osazone is obtained from d-fructose as from d-glucose. It is therefore evident that the configuration of the molecules of these hexoses differ only in the ketone group and its adjacent terminal carbon atom. The identity of the osazones serves to confirm the idea that in glucose the α-carbon atom and in fructose the terminal carbon atom react with a second molecule of phenylhydrazine after hydrazone formation has taken place. In other words, it is definite evidence that in the osazones the two phenylhydrazine groups are united to adjacent carbon atoms. The osazone from these two sugars, which may properly be called glucosazone or fructosazone, has the following constitution:



$$\begin{array}{l} CH_2OH \\ | \\ (CHOH)_3 \\ | \\ C=N{-}NH{-}C_6H_5 \\ | \\ CH=N{-}NH{-}C_6H_5 \end{array}$$

Glucose may be converted into fructose by warming the osazone with hydrochloric acid. The two phenylhydrazine groups are separated by hydrolysis and there results an *osone*, a compound containing an aldehyde and a ketone group:



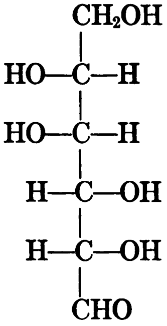
$$
\begin{array}{llcll}
CH_2OH & & & CH_2OH & \\
| & & & | & \\
(CHOH)_3 & & & (CHOH)_3 & \\
| & & & | & \\
C=N-NHC_6H_5 & HOH & & C=O & H_2N-NH-C_6H_5 \\
| & + & \rightarrow & | & + \\
CH=N-NHC_6H_5 & HOH & & CHO & H_2N-NH-C_6H_5 \\
\text{Osazone} & & & \text{Osone} & \text{Phenylhydrazine}
\end{array}
$$

On careful reduction the aldehyde group is reduced to a primary alcohol and fructose is formed. This reaction is general for the conversion of aldoses into ketoses.

In harmony with what has been said regarding which two carbon atoms react in the formation of the osazones, it is found that while d-glucose and d-mannose yield different hydrazones they yield the same osazone. It has been shown already that the molecules of these sugars differ only in the positions occupied by the H and OH linked to the α-carbon atom (**152**).

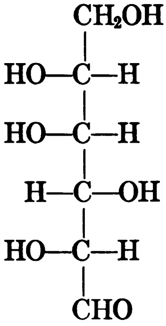
Heptoses, octoses, and nonoses, aldoses containing seven, eight, and nine carbon atoms, have been prepared by Fischer from the hexoses by the cyanhydrin synthesis. These compounds are not found in nature. It is of biological interest that they are not fermentable by yeast.

157. Special Properties of the Hexoses. — Among the many possible aldo- and keto-hexoses, there are only four which are of great importance as natural products:



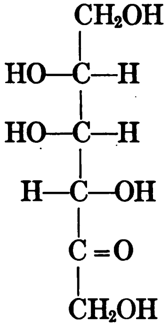
$$\begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CHO}\end{array}$$

d-mannose



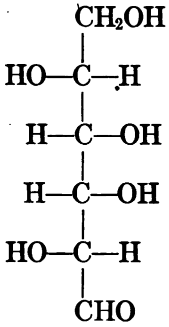
$$\begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CHO}\end{array}$$

d-glucose



$$\begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{C{=}O}\\ |\\ \mathrm{CH_2OH}\end{array}$$

d-fructose



$$\begin{array}{c}\mathrm{CH_2OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{CHO}\end{array}$$

d-galactose

Mannose is seldom found in nature as such and only in small amounts. It forms in plants a cellulose-like substance, mannocellulose (mannan), in the cell walls, and in this form occurs in large quantities, an especially good source being the ivory nut. Mannose is obtained as a hard, solid amorphous mass which is deliquescent and dissolves easily in water, slightly in alcohol and is insoluble in ether. It is identified as the phenylhydrazone which melts at 195–200°.

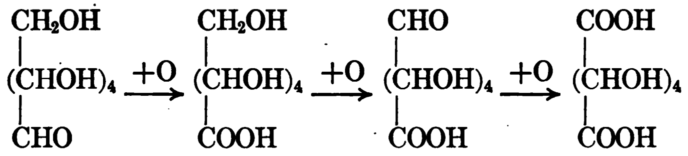
On reduction with nascent hydrogen mannose is converted into the hexahydric alcohol, *mannite*. The latter is found in considerable amounts in manna, that from the ash containing 30–60 %. Mannose is easily fermentable by yeast. It is crystalline and melts at 132°.

d-glucose (dextrose, grape sugar) is found widely distributed with fructose in ripe fruits and other parts of plants, including the nectar of flowers. It is formed from the hydrolysis of cane sugar, malt sugar, and milk sugar, starch, etc. It is the sugar which is a normal constituent of the blood and lymph, being present to 1 part in 1000. In diabetes, a disease of the pancreas, it occurs in the urine sometimes in large amounts.

On reduction of glucose the hexahydric alcohol d-sorbite is formed, and on oxidation gluconic acid, analogous to mannonic acid, and on further oxidation the dibasic saccharic acid, analogous to manno-saccharic acid.

d-glucose crystallizes from alcohol in water-free form, and from water as a hydrate, $C_6H_{12}O_6 + H_2O$. Water-free glucose melts at 146° and at 170° loses water from its H and OH groups, several molecules of glucose condensing to a polysaccharide *glucosan.* By treating glucose with dehydrating agents, such as strong acids, several molecules are condensed to form polysaccharides, complexes having a high molecular weight.

On oxidation of d-glucose the aldehyde group is first attacked and is converted into *gluconic* acid, and on further oxidation the primary alcohol group is converted successively into an aldehyde and then into a carboxyl group:



$$\begin{array}{l} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CHO \end{array} \xrightarrow{+O} \begin{array}{l} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ COOH \end{array} \xrightarrow{+O} \begin{array}{l} CHO \\ | \\ (CHOH)_4 \\ | \\ COOH \end{array} \xrightarrow{+O} \begin{array}{l} COOH \\ | \\ (CHOH)_4 \\ | \\ COOH \end{array}$$

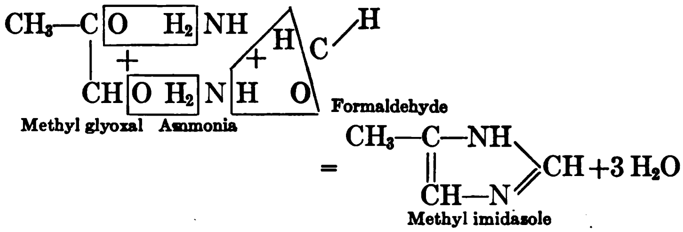
d-glucose d-gluconic acid d-glycuronic acid Saccharic acid

Although this is the course of the oxidation of glucose in the laboratory, and although animals regularly oxidize large amounts of glucose, these acids do not represent the course of the first steps in the destruction of sugar by the living organism. Instead the glucose molecule is dissociated into simpler compounds containing but three and two carbon atoms, and it is these which are oxidized. The first step in the biological degradation of the sugars is therefore not oxidative but hydrolytic (**164**).

d-glucose is the most easily utilized of the hexoses. In healthy persons the capacity to utilize this sugar is as great as the capacity of the digestive tract to absorb it. Healthy young men have been known to absorb more than a pound of glucose within twenty-four hours without the appearance of sugar in the urine. It is likewise easily fermented by yeasts, in which process it is converted into alcohol and carbon dioxide (**164**). Glucose is manufactured on a commercial scale by the acid hydrolysis of starch.

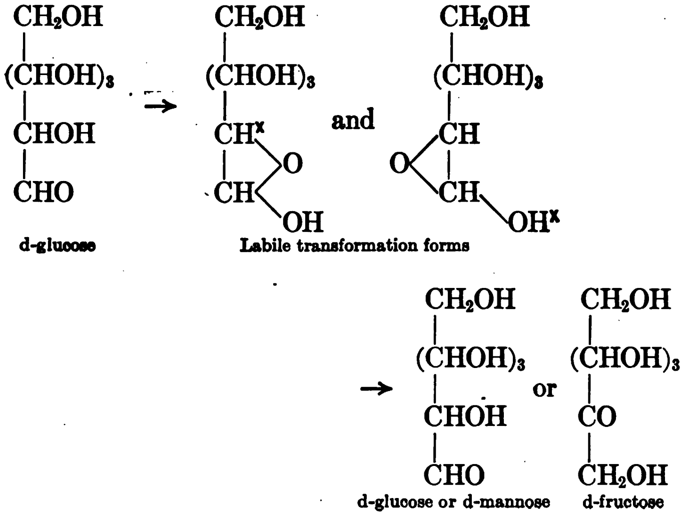
Action of Alkalies on Glucose. — When allowed to stand for several months with dilute alkali glucose is converted to the extent of 50–60% into inactive lactic acid, .5–2% into formic acid, and 30–50% into several hydroxy acids. Among other cleavage products formed by alkalies is *methyl glyoxal*, the aldehyde of pyruvic acid.

A reaction of biological interest is the formation of *methyl imidazole* by the action of ammonia and zinc hydroxide on glucose. This illustrates in a suggestive way the possibility of the formation of certain cyclic compounds within the animal body through the participation of carbohydrate. It will be recalled that one of the amino acids, histidine (**138**), derived from proteins, contains the imidazole ring. The formation of methyl imidazole from glucose and ammonia is best explained as the result of the interaction of ammonia with the dissociation products of glucose, methyl glyoxal, and formaldehyde:



In solution in water containing the slightest trace of alkali (OH ions), glucose is in part transformed into d-fructose and d-mannose. The explanation of this change, first studied by de Bruyn and van Ekenstein is as follows:

The aldose d-glucose, in water solution passes to some extent into the forms illustrated by the following structural formulæ:

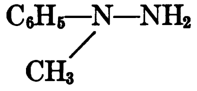


The change is believed to take place through the lability of one hydrogen atom marked **x** in the intermediate forms whereby it can wander from one to the other of the two neighboring carbon atoms. By the shifting of a hydrogen from the end carbon atom to the second an aldose would be regenerated, but by the law of chance the hydroxyl group would take its place on one side of the chain as frequently as the other, and d-glucose would be regenerated or d-mannose would be formed accordingly. By a shifting of the hydrogen atom from the second to the end carbon atom a ketone sugar d-fructose would result. When therefore any one of the three sugars d-glucose, d-mannose, or d-fructose is in solution in the presence of a low concentration of hydroxyl ions, it will pass in part into the other two, until a certain proportion exists among the three kinds of molecules, *i.e.* each form is in dynamic equilibrium with the other two. If by some means the glucose is removed from the system, more will be formed.

This observation is of the greatest importance in that it enables us to understand how an animal may absorb from the digestive tract mannose or fructose and yet these never be present in the blood. They are always transformed into d-glucose if the absorption is not too rapid, in which case the fructose and mannose are said to exceed the assimilation limit since they escape into the urine.

d-glucose yields a phenylhydrazone which melts at 144–146°, and an osazone which melts at 206°. On reduction it yields the hexahydroxy alcohol d-sorbite.

d-fructose is actually levorotatory, but is called the dextro form because of its structural relationship to d-glucose. Although d-fructose yields the same osazone as do d-glucose and d-mannose, it is easily distinguishable from these by its peculiar behavior with *methyl phenylhydrazine*:



$$\begin{array}{l} C_6H_5—N—NH_2 \\ \quad\;\; / \\ CH_3 \end{array}$$

With this methyl-substituted phenylhydrazine d-fructose and other ketoses yield osazones. The aldoses, on the other hand, do not react with this reagent beyond the hydrazone stage under ordinary conditions. The methyl phenylosazone of fructose melts at 158–160°.

The capacity of the animal organism to utilize fructose is much less than for d-glucose. d-fructose is easily fermentable by yeast.

An extremely interesting observation is the formation of d-fructose from *d-mannite* by a kind of fermentation induced by *Bacterium xylinum* Brown, through which the alcohol is oxidized to a ketone.

d-galactose is present in milk sugar in union with d-glucose. It also occurs in certain polysaccharides, as agar-agar, and in certain glucosides. It exists in the brain in considerable amount in union with a fatty acid and a base of unknown chemical nature. The hexose itself has never been found in the free state in either plants or animals. Galactose is easily distinguishable from the other hexoses by the insolubility in dilute nitric acid of the dicarboxy acid, *mucic acid,* which results on oxidation of the sugar with nitric acid. Mucic acid is so insoluble and is formed so nearly quantitatively that its formation serves as the best available method of estimating galactose or galactose-yielding polysaccharides.

d-galactose is much less readily utilized in the animal body than is either glucose or fructose, and on the ingestion of even moderate amounts is eliminated in part unchanged in the urine.

158. The Disaccharides. — There are three sugars of great biological interest which yield on hydrolysis two molecules of hexose. The molecular weights of all of them correspond to the formula $C_{12}H_{22}O_{11}$. They are *sucrose,* or cane sugar, which yields on hydrolysis one molecule of d-glucose and one of d-fructose; *maltose,* or malt sugar, which yields two molecules of d-glucose; and *lactose,* or milk sugar, which yields one molecule of d-galactose and one of d-glucose.

Sucrose, $C_{12}H_{22}O_{11}$, occurs in the juices of many plants, especially sugar cane and sugar beet. As much as 16–20 % of the dry substance of the plant is sucrose. It crystallizes readily. The sugar is extracted from the finely rasped beets with warm water and the solution treated with lime, which causes the neutralization of acids in the juice, and is then boiled to coagulate the proteins. The solution is then treated with carbon dioxide to precipitate most of the calcium, and after this with sulphur dioxide whose reducing action discharges the color. It is again boiled and filtered, and the filtrate evaporated under diminished pressure to crystallization. The mother liquor from the crystals is molasses. The molasses yields another portion of sucrose on treatment with lime or strontium hydroxide, an insoluble calcium or strontium *saccharate* being formed. The latter is decomposed by carbon dioxide and the liquid, freed from solid calcium or strontium carbonate, yields a crop of crystals of sugar. The molasses, which contains much glucose, is in great part fermented for the preparation of rum or alcohol for industrial purposes.

Sucrose forms large monoclinic crystals which are easily soluble in water and melt at 160°, then solidify to a glassy mass and on further heating become brown with the formation of caramel. The specific rotation of cane sugar is, for a solution of about 25 % strength:

$$[\alpha]_D = +66.5^\circ$$

The rotatory power is made use of in the estimation of sucrose. On boiling with dilute acids, it is converted into d-glucose and d-fructose. The resulting solution rotates the plane of polarized light to the left, since the levorotatory power of fructose is $[\alpha]_D = -93^\circ$ while for d-glucose or dextrose $[\alpha]_D = +52.7^\circ$. Since the direction of rotation changes when cane sugar is hydrolyzed, the process is called inversion, and the product *invert sugar*.

The same conversion of sucrose into glucose and fructose is brought about by an enzyme *invertase*, which is present in yeast and in the mucous membrane of the small intestine. The rate of inversion of cane sugar by acids has been very carefully studied, and it has been found that it is proportional to the concentration of the hydrogen ions present. The hydrogen ion is therefore the catalytic agent for this hydrolytic reaction.

Sucrose does not reduce the oxides of the heavy metals (*e.g.* Fehling's solution) as do glucose, fructose, mannose, and the other aldoses and ketoses, nor does it form compounds with hydrazines. It does not therefore contain a carbonyl (aldehyde or ketone) group, but on hydrolysis to glucose and fructose an aldehyde and a ketone group are formed. It contains, however, eight hydroxyl groups, since it yields an octa-acetyl derivative.

Sucrose is regarded as a glucoside of d-fructose (**161**). It cannot be utilized directly by an animal, being excreted in the urine when introduced directly into the blood. In the digestive tract it is hydrolyzed into glucose and fructose before absorption.

Maltose, $C_{12}H_{22}O_{11} + H_2O$, is found in small amounts in many plants. It is the end product of the action on starch of the enzyme *amylase* of the saliva of the omnivorous animals, including man. It has been found in human urine in disease of the pancreas, but in the normal organism maltose is readily utilized either when introduced into the alimentary tract or directly into the blood. The blood contains an enzyme *maltase* which converts maltose into two molecules of d-glucose. This change is likewise effected by heating with dilute acids. There is no corresponding enzyme in the blood or tissues for the hydrolysis of sucrose or lactose.

Maltose reduces solutions of the oxides of the heavy metals, which indicates that it contains a carbonyl group. Maltosazone melts at 205°.

Isomaltose is a disaccharide which is formed by the dehydrating action of strong hydrochloric acid on a concentrated solution of glucose. Its osazone melts at 200°

and is more soluble in water than is maltosazone. Its stereochemical configuration is sufficiently different from maltose to make it non-fermentable with yeast. The enzymes of yeast do not hydrolyze it to hexoses, but the enzyme *emulsin* found in the almond converts it into two molecules of glucose.

Lactose or Milk Sugar, $C_{12}H_{22}O_{11} + H_2O$, is found nowhere but in the milk of animals. It contains a carbonyl group, since it reduces certain oxides of the heavy metals. Its osazone melts at 200°.

In the animal organism lactose behaves as does cane sugar. When taken into the alimentary tract, it is hydrolyzed by the enzyme *lactase* into d-glucose and d-galactose before being absorbed; and if introduced directly into the blood, is principally excreted unchanged in the urine. The lactose of the milk is derived from d-glucose and not from the food.

Melibiose is isomeric with lactose and yields the same hexoses on hydrolysis. It results together with d-fructose from the action of dilute acids or of *invertase* upon the trisaccharide raffinose. Like lactose, it is a reducing sugar. It resembles lactose in being hydrolyzed by emulsin, but differs from it in not being cleaved by lactase.

159. The Stereochemical Configuration of the Sugars Determines their Biological Value. — Of the sixteen isomers of the aldohexoses only three are readily utilized by the higher animals, and of these three, d-glucose, d-fructose, and d-mannose, only the former has a high assimilation limit. Galactose is utilized with more difficulty than the three first named.

A similar relationship holds in the case of the disaccharides. Before these can be utilized biologically they must be converted into the C_6 sugars, and there is a marked difference in the extent to which various organisms are prepared with the specific enzymes necessary for their cleavage. Thus the invertase of yeast, but not the maltase and lactase, act on cane sugar. Invertase and lactase do not cleave maltose. Emulsin does not hydrolyze any of these disaccharides. Certain of the molds are provided with all of these enzymes.

The limitations of the digestive tract are similar to those of yeasts. The mucous membrane of the intestine in all animals contains invertase and maltase and usually lactase. The blood contains maltase, but no invertase or lactase.

Yeasts show among the races great variation in their capacity to effect the hydrolysis of the disaccharides. Thus, the yeast which induces alcoholic fermentation of milk, forming *kephir,* contains lactase, while beer yeast does not. The latter, however, can cleave cane sugar and ferment the resulting sugars. Many yeasts contain both invertase and maltase, and can ferment both these sugars, but *Saccharomyces Marxianus* contains only invertase and can ferment therefore sucrose, but not maltose. *Saccharomyces octosporus,* on the other hand, can ferment maltose but not sucrose, and *Saccharomyces apiculatus,* which is capable of fermenting d-glucose, d-mannose, and d-fructose, contains no enzyme for the hydrolysis of any of the disaccharides, and cannot ferment the latter.

160. Raffinose, $C_{18}H_{32}O_{16}$—$5\,H_2O$, is a trisaccharide found in small amount in the sugar beet and therefore in considerable amount in molasses. It is especially plentiful in the cotton seed (10 %) and is a constituent of *Eucalyptus manna.* On hydrolysis with dilute acids it is first converted into fructose and melibiose, and the latter into d-glucose and d-galactose. Top yeast effects the cleavage of raffinose into d-fructose and melibiose, and bottom yeasts ferment it completely. Emulsin converts raffinose into galactose and cane sugar.

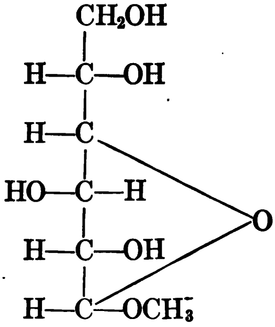
THE GLUCOSIDES

161. In a manner analogous with the reaction of the aldehydes with alcohols to form acetals (**32**), the aldoses can react with alcohols to form the glucosides. Many such compounds occur in nature in plants, these usually containing an aromatic alcohol, aldehyde, or acid, but also other classes of compounds. The carbohydrate group is in most cases glucose, but glucosides are also known which yield galactose, rhamnose, and disaccharides. The leaves of *Indigofera tinctoria* and of *Isatis tinctoria* contain a glucoside *indican,* from which the dye indigo results by a process of fermentation. The madder root contains among other glucosides *ruberythric acid,* which yields the red dye *alizerin.* The leaves of *Digitalis purpurea* yield the glucoside *digitalin,* which exerts a peculiar action on cardiac muscle. Willow bark contains salicin, from which salicylic acid (**209**) is derived. The roots of fruit trees, as apple, peach, etc., yield the glucoside *phlorizin,* which is much employed in inducing an experimental glycosuria in animals for biochemical studies. The roots of Spiræa contain *gaultherin*, mustard seeds yield *myrosin*, etc.

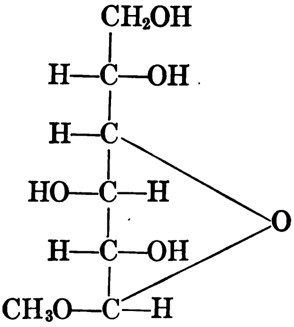
One of the best known of the glucosides is *amygdalin*, from the bitter almond. Solutions of amygdalin do not reduce solutions of the heavy metals, a fact which is taken to indicate that there is no free aldehyde group. After hydrolysis with dilute acids the presence of glucose can be detected by the reduction of Fehling's solution, and by the formation of an insoluble osazone (p. 286) which melts at 205°. Benzaldehyde can be detected by its odor, and HCN by its precipitate with silver nitrate. It is soluble in alcohol and can be crystallized from this solvent. Emulsin, an enzyme contained in the almond, hydrolyses amygdalin into benzaldehyde (**204**), hydrocyanic acid, and two glucose molecules. Water extract of beer yeast contains an enzyme which splits off hydrolytically but one molecule of glucose and leaves the combination benzaldehyde, hydrocyanic acid, and glucose, the glucoside of mandelic acid nitrile (**206**).

CONSTITUTION OF THE GLUCOSIDES

The best-known synthetical glucosides are those from glucose and methyl alcohol. When a concentrated solution of d-glucose in methyl alcohol is treated with gaseous hydrochloric acid, there result two compounds known as α-methyl glucoside and β-methyl glucoside. The α-form is dextrorotatory and is soluble in 200 parts of alcohol; while the β-form is levorotatory and is soluble in 66.7 parts of alcohol at 100°. They can therefore be separated by their different solubilities. Maltase hydrolyzes the α-glucoside but not the β-form, while emulsin hydrolyzes the β-form but not the α-form. The natural glucosides are in general hydrolyzed only by emulsin, and for this reason they are termed β-glucosides. The structural formulæ assigned to α- and β-methyl glucosides are as follows:



α-Methyl glucoside

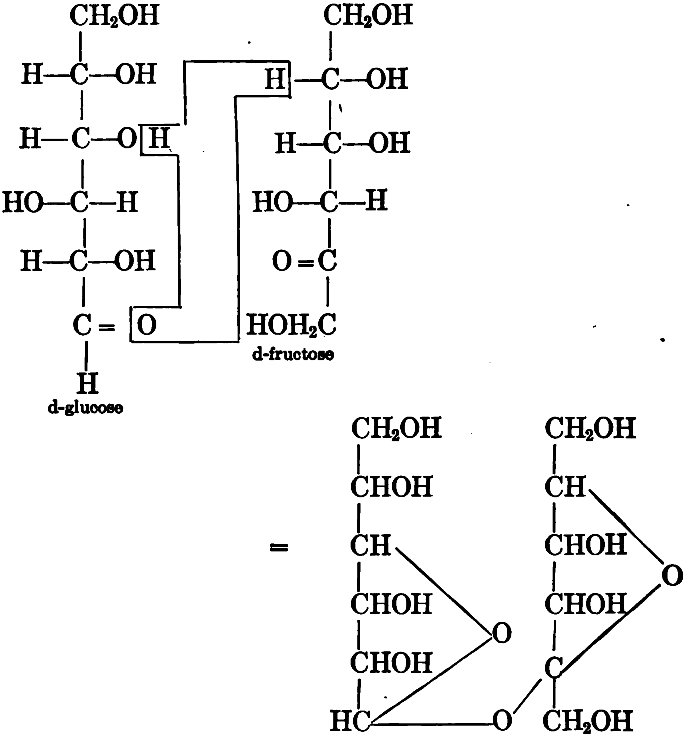


β-Methyl glucoside

The reasons for assigning these constitutional formulæ are the following:

1. Only a single molecule of alcohol reacts with one of glucose, with the elimination of a molecule of water. One of the secondary alcohol radicals must therefore enter into the reaction. This is in all probability the γ-hydroxyl group, since this is the one which reacts in the formation of lactones (**125**), and since no compounds other than those containing γ-hydroxyl groups form glucosides. The ease with which the glucosides are decomposed by hydrolysis argues strongly against the union of the alcohol radical directly to carbon, and for the assumption of linkage through oxygen as in the ethers. The mechanism of glucoside formation may therefore be represented thus:

Sucrose, which contains no carbonyl group, is represented as:



d-glucose

d-fructose

Sucrose

Emil Fischer has suggested the comparison of the specific action of enzymic action in the hydrolysis of sugars and other compounds, with the relationship between lock and key. The stereochemical structures of both the enzyme and the molecules of the substrate determine whether they can interact. This specificity of ferment action is of the greatest significance for the life of the animal or plant cell.

The union of galactose in the galactolipins of the brain and of ribose in nucleic acids is probably of the nature of glucosides.

THE POLYSACCHARIDES

162. Starch $(C_6H_{10}O_5)_n$ (*amylum*) is a non-crystalline carbohydrate produced by plants as a reserve material. It is closely related to cellulose on the one hand, a compound whose peculiar properties fit it to be the skeletal tissue of plants, and to the simple hexoses and disaccharides on the other, into which it is readily converted by hydrolysis. Starch is insoluble in water and exists in grains, tubers, fruits, etc., in the form of grains. These consist of at least two kinds of carbohydrates: *granulose,* which is colored blue by iodine, and starch cellulose, which is not. The blue color produced by iodine is discharged on heating but reappears on cooling. Starch has a very high molecular weight (32,000) and when boiled with water undergoes incipient hydrolysis and is changed into *soluble starch.* The latter forms an opalescent colloidal solution.

The amylase of the saliva of certain animals rapidly causes hydrolysis of starch into a series of simpler carbohydrates, the dextrines, the final product being maltose. Acid hydrolysis converts starch into d-glucose.

The form and appearance of the starch grains vary with their origin. It is a simple matter for one familiar with the forms to identify by microscopical methods the source of the starch.

Starch is not the first product of the synthetic activity of the plant. The latter absorbs carbon dioxide from the air and water and inorganic salts, including nitrates, from the soil. It is generally assumed, since formaldehyde is present in minute amounts in functioning leaves, and, as pointed out earlier (**151**), is polymerized to a mixture of hexoses, that it is the first product formed:

$$CO_2 + H_2O = HCHO + O_2$$

$$6\ HCHO = \underset{\text{glucose}}{C_6H_{12}O_6}$$

The formation of starch is not dependent on the formation of glucose. Leaves which have been kept in the dark until they are starch-free and then in the dark are floated on sugar solutions quickly form starch. d-glucose and d-fructose are most readily utilized for this purpose, but certain plants can use mannose and even galactose for starch synthesis. Stereochemical transformation is, of course, necessary in these cases.

Starch is easily hydrolyzed by acids, but only with great difficulty by alkalies.

Dextrines correspond to the same empirical formula as starch, but their molecular weight is much smaller. It is assumed that there are a large number of dextrines of different molecular complexities, but only two can be readily distinguished. *Erythrodextrine,* which gives a red color with iodine, is first formed by the action of amylase on starch; and *achroodextrine,* which gives no color with iodine, is formed somewhat later.

Cellulose is much more resistant than is starch. It is not acted upon by enzymes formed by the higher animals or plants, and is not easily decomposed by acids or alkalies. On treatment with strong acids under appropriate conditions the only product of its hydrolysis is d-glucose. Cellulose is found nearly pure in the cotton fiber, in linen, and in hemp, and is the principal constituent of wood. The latter, however, contains about half its dry weight of incrusting substances, known as lignin, pectins, and gummy substances.

There occurs in the covering of the tunicata, a group of animals, a polysaccharide *tunicin* which appears to be identical with cellulose. This is the only instance of the occurrence of cellulose in the animal kingdom.

When acted upon by concentrated nitric acid or by a mixture of nitric and sulphuric acids, cellulose is nitrated. According to the conditions, from one to six nitro groups are introduced in ester linkage for each of the $C_6H_{12}O_5$ complexes in the molecule. A mixture of tri- and tetranitrates dissolved in a mixture of alcohol and ether constitutes *collodion.*

Guncotton, or pyroxylin, is the hexanitrate of cellulose. When dissolved in acetone or ethyl acetate and the solution evaporated, the residue in granular form constitutes smokeless powder. A mixture of cellulose hexanitrate with nitroglycerine and other substances forms ballistite, cordite, blasting gelatin, etc.

Cellulose forms several acetates when treated with glacial acetic acid and acetic anhydride in the presence of strong sulphuric acid. These are insoluble in water, but soluble in various organic solvents. Artificial guttapercha is produced by evaporating a solution of tetra-

inal constituent of
lysis. They are
by alkaline copper
the pentoses, they

fruit juices which cause
, beets, and rhubarb are
stituents. Their chemistry
reparations of pectins made by
d yield both pentoses and hexoses,
which seem to be of the type of

es are substances which swell in water and
ous solutions. As examples may be cited
ilage, and those of the roots of salep and
hey yield both pentoses and hexoses on hydrol-
their chemistry has not been thoroughly studied.
ms contain the salts of as yet unidentified organic
and yield these acids and certain reducing sugars on
hydrolysis. Arabinose, xylose, fucose, and galactose
have been identified.

Glycogen is a polysaccharide contained in animal and in certain plant tissues which resembles soluble starch in certain respects, but gives a reddish color with iodine. It is soluble in cold water, forming an opalescent solution. It is formed by the condensation of a number of molecules of glucose, water being separated in the union of each two molecules. It is acted upon by *amylase,* which converts it into maltose as in the case of starch.

The glycogen content is higher in the liver than any acetyl cellulose in acetone. When a solution acetate in glacial acetic acid is poured int precipitate is formed which contains much burns without melting or leaving an ash an "solid alcohol."

Cellulose is indigestible in the alimentary t mals, but certain bacteria present there fer the formation of carbon dioxide, methane, hy formic, acetic, butyric, valerianic, and other tain molds and saprophytic plants secrete *cytase,* which dissolves cellulose. The product not known.

Cellulose is insoluble in all ordinary s dissolves in an ammoniacal solution of c (Schweitzer's reagent), and in a solution of in hydrochloric acid.

Hemicelluloses are important constituents and stony seeds of fruits, coconut rind, et present in considerable amounts in the seeds (pea, bean, etc.). On hydrolysis with acid mannose, and those of the legumes especial A certain amount of arabinose and xylose is formed. They are not well-characterized therefore, and appear to be either mixtures xylan, araban, galactan, or complex carbohy posed of complexes representing several kin

Pentosans are polysaccharides which corres celluloses, but they yield on hydrolysis a pe Thus *xylan,* which is present in the straws to 18–28 %, yields xylose; and *araban,* which occ

other tissu… …group is on one or
fed animal… …the compound may
found in… …. That the amino
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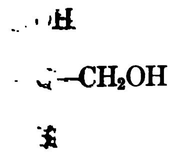
Glucosamine

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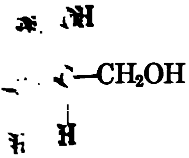
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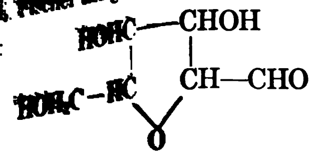
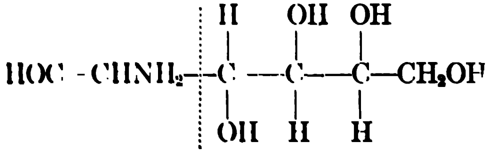
…amine with nitrous acid the amino …by hydroxyl. The resulting hexose is …or mannose. It is known as *chitose*. …and does not yield a difficultly soluble …comparison with the synthetically prepared …Fischer assigned to chitose the following cyclic …:

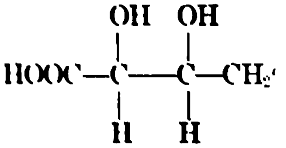

Chitose

l… …is a polysaccharide entirely analogous to starch, which is found as a reserve carbohydrate in dahlia roots and other tubers of the Compositæ. On hydrolysis it yields only d-fructose. In the plant tissues where inulin occurs there is formed an enzyme, *inulase,* which effects its hydrolysis whenever growth begins. There is no inulase in the digestive secretions of animals and therefore no provision for the utilization of this carbohydrate.

It is not certain whether the amino group is o the other side of the carbon chain, and the compo be either glucosamine or mannosamine. That group is united to the carbon atom neighbori hyde is made highly probably by the decom scribed by Neuberg, of glucosamine into er (150) by boiling with barium hydroxide.

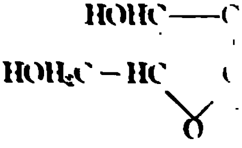


$$HOC-CHNH_2-\overset{H}{\underset{OH}{C}}-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CH_2OH$$



$$HOOC-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CH_2$$

On treatment of glucosamine with group is replaced by hydroxyl. T however not glucose or mannose. It does not ferment, and does not osazone. By comparison with th ecte compound, Fischer assigned to ci s the structure: y prod



Chitos

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Inulin $(C_6H_{10}O_5)_n$ is a poly application i to starch, which is found a the yeast in

CHAPTER XV

THE CHEMICAL CHANGES IN
OF THE SUG

164. The nature of the ch
the fermentation of sugars has ociation and re-
gated, and the mechanism of When alkali acts on
alcohol is fairly definitely u the extent of 54 per
the method of investigatio acid to .5–2 per cent,
of the compounds which droxy acids containing
glucose by chemical age 1 per cent of alcohol
induce decompositions is no glycollic or oxalic
a certain type of ferr ned. If lactic acid were
certain degree of pr arbon chain into two three-
glucose molecule by ent oxidation and reduction,
those on which sug be optically active, which
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change. some three-carbon aldehyde
On the other first formed.
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yeast to ta $CO—COOH$
process of $—CO—CHO$
process of $CH_2OH—CHOH—CHO$
which ca $CH_2OH—CO—CH_2OH$
mediary the most probable intermediary
into al
An cleavage products.
insta Methyl glyoxal is not fermentable by yeasts, while the
are positive for glyceraldehyde and dihydroxy

actory explanation is probably

$$OH + 4H$$

$$CHO + 2CO_2$$

$$—C_2H_5OH$$

support from the new well-
that yeast juice free from living
enzyme, carboxylase, which accelerates
of pyruvic acid into acetaldehyde and
Acetaldehyde is readily reduced to alcohol.
ther theory of alcoholic fermentation deserves to be
tioned. Schade showed that lactic acid treated with dilute sulphuric acid formed acetaldehyde and formic acid:

$$CH_3—CHOH—COOH = CH_3—CHO + H—COOH$$

showing a tendency for this line of cleavage which might be accelerated by a yeast enzyme. Formic acid is rapidly decomposed catalytically by means of metallic rhodium into hydrogen and carbon dioxide. Schade held that the latter reaction might also be catalyzed by a ferment, thus producing through lactic acid as a first product from hexose, acetaldehyde, and hydrogen in a nascent state to reduce it, together with one molecule of carbon dioxide for each molecule of alcohol produced. This is the proportion actually observed in yeast fermentation. Yeasts do not however ferment a mixture of acetaldehyde and sodium formate.

This cannot therefore be considered a very probable explanation of what takes place in the animal body.

The most plausible hypothesis yet advanced concerning the biological method of forming fats is that of Smedley, who condensed croton aldehyde with pyruvic acid, and by oxidizing the resulting ketonic acid with hydrogen peroxide, CO_2 was split off and the doubly unsaturated *sorbic acid* was formed:

$$1.\ \underset{\text{Croton aldehyde}}{CH_3—CH=CH—CHO}+\underset{\text{Pyruvic acid}}{CH_3—CO—COOH}$$
$$=CH_3—CH=CH—CH=CH—CO—COOH$$

$$2.\ CH_3—CH=CH—CH=CH—CO—COOH+O$$
$$=\underset{\text{Sorbic acid}}{CH_3—CH=CH—CH=CH—COOH}+CO_2$$

It is easy to understand how the double bonds could be removed from such an acid by reduction.

Smedley suggests pyruvic acid and acetaldehyde as the starting point for fat synthesis in the body. The following reactions will illustrate the process:

$$1.\ \underset{\text{Pyruvic acid}}{CH_3—CO—COOH}+\underset{\text{Acetaldehyde}}{CH_3—CHO}$$
$$=CH_3—CH\boxed{OH}—CH\boxed{H}—CO—COOH$$

$$2.\ \underset{\text{Pentylenic α-keto acid}}{CH_3—CH=CH—CO—COOH}+O$$
$$=\underset{\text{Crotonic acid}}{CH_3—CH=CH—COOH}+CO_2$$

$$3.\ CH_3—CH=CH—COOH+2\,H$$
$$=\underset{\text{Butyric acid}}{CH_3—CH_2—CH_2—COOH}$$

CHAPTER XVII

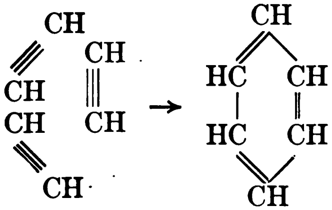
THE AROMATIC COMPOUNDS

166. The hydrocarbons of the aliphatic series, or the fatty compounds, are not products of animal or plant metabolism, with the exception of methane, which results from the bacterial fermentation of cellulose. None of them have highly agreeable odors. There are in certain products of vegetable origin compounds which contain only carbon and hydrogen, and are very poor in hydrogen, suggesting compounds of a highly unsaturated character, as isoprene (**82**). These differ in every respect in their properties from the unsaturated or the saturated hydrocarbons of the aliphatic series. Thus *toluene,* C_7H_8, from Tolu balsam, and *cymene,* $C_{10}H_{14}$, from oil of eucalyptus, oil of thyme, oil of caraway, and other *essential oils,* are hydrocarbons of pronounced and characteristic aromatic odors. They do not form addition products with the halogens as do the unsaturated hydrocarbons. *Benzoic acid,* which is found in gum benzoin, in cranberries, and elsewhere in plants, yields when its calcium salt is subjected to dry distillation, a hydrocarbon, C_6H_6, *benzene.*

Toluene is oxidized to benzoic acid and is therefore closely related to benzene. Cymene yields on oxidation a dibasic acid, *teraphthalic acid,* which on distillation of its calcium salt likewise yields benzene.

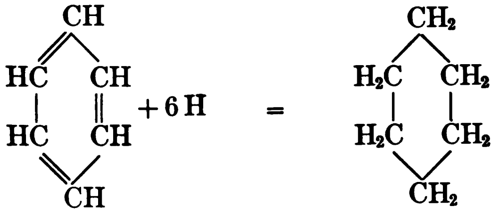
Benzene may be regarded as the mother substance of a large number of compounds of great biological and technical interest, and its chemistry should be considered in some detail. The constitution of its molecule was first suggested by Kekulé in 1867, and was based principally on the following evidence: Since benzene does not behave like an unsaturated compound, its structure must be of a special nature to account for this property, for it is not possible to write the formula C_6H_6 as an open chain without the employment of double or triple bonds. It has therefore a closed ring structure.

Benzene is formed when acetylene is passed through a heated tube or subjected to high pressure. The molecular weight is 78, so it follows that in the polymerization three molecules of acetylene condense into one:



Benzene (Kekulé formula)

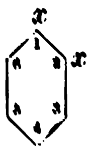
The correctness of the view that the benzene molecule represents a closed ring of six carbon items linked alternately by single and double bonds is supported by the observation that when the vapors of benzene mixed with hydrogen are passed through a heated tube containing finely divided nickel, six atoms of hydrogen are absorbed and hexamethylene (**112**) is formed:



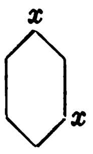
Benzene Hexamethylene

Kekulé also emphasized the fact that *all of the six hydrogen atoms of benzene are equal*, since each is attached to a carbon which is alternately singly and doubly bound, *i.e.* to carbon atoms which are alike. If this is true there should be but one mono-substitution product of benzene as chlor, brom, nitro, amino, etc., benzene, all of which derivatives are known. Actually but a single compound of these types is known. On the normal aliphatic hydrocarbon containing six carbon atoms, three isomeric mono-substitution products exist, depending on whether the substituting group is at 1, 2, or 3, $C—C—C—C_3—C_2—C_1$

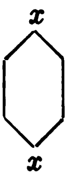
On the other hand, theory calls for three disubstitution products of such a hexagonal ring, and three dichlor, dinitro, dihydroxy, etc., benzenes, but no more than three, are known. These are called *ortho-*, *meta-*, and *para-* derivatives (designated as o-, m-, and p-) according



Ortho



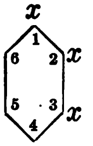
Meta



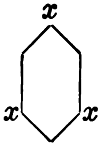
Para

to whether the substituting groups occupy positions on neighboring carbon atoms (1 : 2) or on atoms separated by one (1 : 3) or by two carbon atoms (1 : 4) respectively. The position 1 : 5 is the same as 1 : 3 and 1 : 6 is the same as 1 : 2. The number of isomers should be the same for disubstitution products whether these are similar or dissimilar.

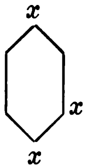
There should be, according to theory, three isomers of a trisubstitution product of benzene provided all substituting groups are similar, but more if two are similar and one dissimilar.



Adjacent or vicinal
(1:2:3)



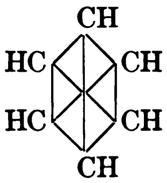
Symmetrical
(1:3:5)



Unsymmetrical
(1:3:4)

Of the vast number of derivatives of benzene which have been prepared and studied, theory has in all cases accorded with observation.

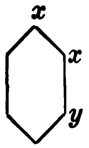
It is essential, if we accept this structure for benzene, to assume that the double bonds are alternating between the 1 : 6 and the 1 : 2 positions, otherwise there should be observed different properties for a disubstitution product in which the groups were separated by a single and double bond respectively. Such a vibration was assumed by Kekulé. To obviate this difficulty, since but one ortho disubstitution product has been observed, the *centric formula* was proposed by Armstrong. According to his assumption the fourth bond of each carbon atom in the ring is directed toward the center:



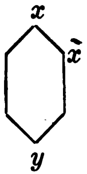
Such a structure accounts for the extreme stability of benzene, which is much greater than that of the aliphatic hydrocarbons, and also accounts for the peculiar isomerism of its derivatives and for its "aromatic" character. The six-membered ring is referred to as the benzene nucleus, and since many derivatives of benzene are known in which one or more aliphatic groups replace the hydrogen atoms of the nucleus, these are called "side chains." Substitution can be effected either in the nucleus or in the side chain.

DETERMINATION OF POSITION OF SUBSTITUTING GROUPS IN THE NUCLEUS

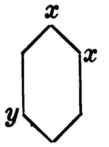
167. This has been determined by very extensive and elaborate study for a few substitution products of benzene by a method, the principle of which was enunciated by Körner. It depends upon the fact that when a third substituent y is introduced into an *ortho* compound, in which both substituting groups are similar, *but two isomers can be formed.* This is true whether y is like or unlike x:



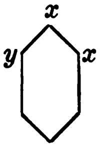
(1)



(2)

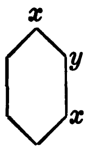


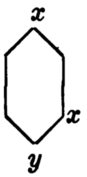
(3)

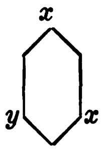


(4)

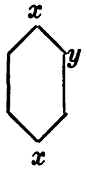
Two and 3 are the same and 1 and 4 are the same. In the case of the *meta* compound *three isomers can be formed*:







While in the case of a *para* compound *but one* trisubstitution product can result:



No matter what position y may take, it occupies the same relative positions with respect to the other substituents, viz. it is always in the ortho- position to one and in the meta position to the other. The experimental evidence in support of the theory of structure consists in the preparation of compounds having the percentage composition called for by the theory and efforts to separate the product by crystallization, distillation, etc., into fractions which have the same composition, but different physical properties; *i.e.*, isomers. The fact that patient search has revealed the existence of all the isomers demanded by theory, *and in no instance more than these,* is convincing evidence of the validity of the theory.

Benzene, C_6H_6, is a colorless liquid with a characteristic odor, which boils at 80°. When strongly cooled it crystallizes, the crystals melting when warmed to 5.4°. Its specific gravity at 20° is .874. It burns with a smoky flame and its vapors are inflammable. It dissolves in all proportions in alcohol or ether, but is insoluble in water. It dissolves fats, resins, etc., and is a good solvent for sulphur, phosphorus, iodine, and many other substances.

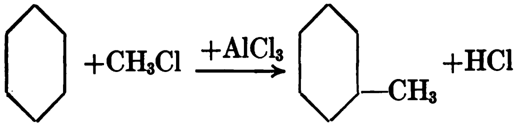
The benzene of commerce, also called *benzole,* was formerly obtained from coal tar, which on distillation yields in the fraction obtained up to 150°, from 3–5 per cent of a mixture of benzene and its homologues, *toluene* and *xylene.* Recently Rittmann has perfected a process by means of which the aliphatic hydrocarbons of petroleum can be made to yield 10–15 per cent of these cyclic hydrocarbons. This process consists in heating the petroleum under pressure for a time, and then distilling the product. The principle involved depends upon the *dissociation* of the aliphatic hydrocarbons under these conditions into various unsaturated hydrocarbons, among which are a small content of acetylene and of its alkyl derivatives (see p. 164). At high temperatures and pressures acetylene condenses to benzene, an irreversible reaction.

PHYSIOLOGICAL PROPERTIES OF BENZENE

168. The aliphatic and aromatic hydrocarbons show considerable differences in their physiological properties. The lower members of the methane series produce sleep if inhaled, and death by asphyxia. The toxicity increases as the carbon atoms become more numerous. Hexane is actively intoxicant, producing a long stage of excitement followed by deep anæsthesia. It acts on the sensory side. Benzene and other aromatic hydrocarbons act principally on the motor centers, producing convulsions and paralysis. Benzene has furthermore a selective toxic effect for the white blood corpuscles, producing leucopenia, and is employed in medicine in cases of leucæmia.

HOMOLOGUES OF BENZENE

169. Friedel and Crafts Reaction. When benzene is treated with an aliphatic halogen compound in the presence of aluminum chloride a reaction takes place in which hydrochloric acid gas is evolved and the aliphatic group is linked to the benzene nucleus:



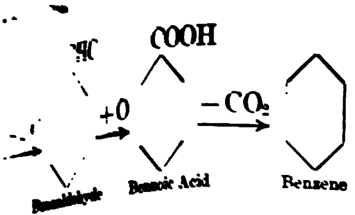
For the sake of simplicity the hexagonal ring is employed to represent benzene.

By the employment of the homologues of methyl chloride, ethyl, propyl, etc., groups can be substituted for a hydrogen atom in the benzene ring. The benzene nucleus

the same composition, but differen
isomers. The fact that pa
the existence of all the isom
in no *instance more than t*
of the validity of the theor

Benzene. C_6H_6. is a colorless liquid
which boils at 80°. Wh ... sep-
the crystals melting ... is much
gravity at 20° is
flame and its vapors ... CrO_2Cl_2, it is
in all proportions in a ... side chain," the
in water. It dissol ... HO, called *benzal-*
a good solvent for sulphu ... yl formaldehyde.
many other substances. ... toluene directly

The benzene of commer ... is the acid corre-
merly obtained from coal ... be regarded as phenyl
in the fraction obtained ... on heating the cal-
a mixture of benzene ... oxide is removed from
xylene. Recently Ritt ... formed. The follow-
means of which the ... illustrate the general
leum can be made to ... containing both an aromatic
hydrocarbons. Th
leum under press
product. The
dissociation of
conditions into
which are a s
derivatives (se
sures acetyle
reaction.



side chains as in ethyl-, propyl-, isopropyl-, etc.,
no matter how many carbon atoms con-

Hence the three deriva-
nzoic acid.

it is obvious that derivatives
produced by the action of chlorine
rivatives in which the chlorine occu-
meta- or *para-* position to the methyl
benzene nucleus, or those in which one, two
the hydrogen atoms in the methyl group are
ed by chlorine. The position taken by chlorine
n it reacts with toluene depends upon the conditions
der which the reaction takes place. At low temper-
tures and in the absence of light ortho- and para-chlor toluenes are formed in about equal proportions, with very little of the meta- compound. When Cl acts on p-toluidine (**176**) the Cl enters the m- position to the CH_3 group. The action is greatly accelerated by the presence of halogen carriers, such as iodine, ferric chloride, antimony trichloride, etc.

At high temperatures (110°) even in the absence of light chlorine substitutes in the side chain exclusively. In the presence of halogen carriers, however, the chlorine enters the nucleus even at high temperatures.

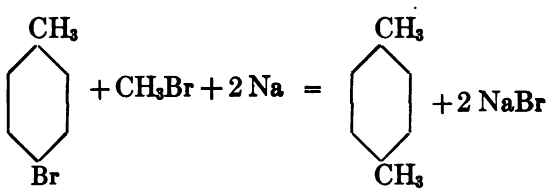
At ordinary temperatures in direct sunlight the chlorine enters the side chain exclusively.

The terms chlor-, brom-, and iodo-toluenes refer to the o-, m-, p-, derivatives. The derivatives in which the halogen is in the side chain are named as follows:

$C_6H_5CH_2Cl$	$C_6H_5CHCl_2$	$C_6H_5CCl_3$
Benzyl chloride	**Benzal chloride**	**Benzo trichloride**

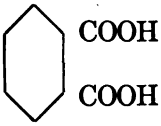
The group $C_6H_5—CH_2—$ is called the benzyl-radical; $C_6H_5CH =$ benzal-, and $C_6H_5C \equiv$ benzo-, radical. The behavior of these will be further described later.

171. Xylenes. Dimethyl, benzenes, $C_6H_4(CH_3)_2$, are formed by the Fittig reaction, employing brom toluenes and methyl bromide:

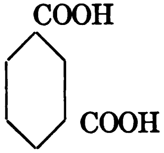


The same result is obtained by means of the Friedel and Crafts reaction (**169**), by means of which all of the hydrogens of the benzene nucleus have been successively replaced by methyl groups.

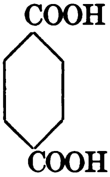
Ortho-, meta-, and para-xylenes can yield by oxidation either monobasic o-, m-, and p-toluic acids, or the three corresponding dibasic acids:



Phthalic acid



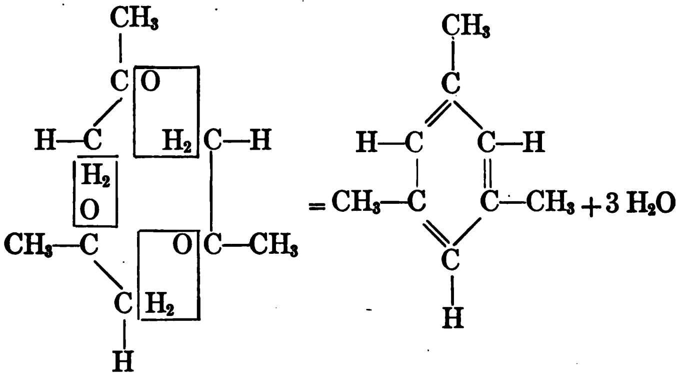
Isophthalic acid



Teraphthalic acid

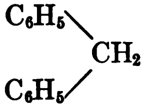
Phthalic acid when heated loses a molecule of water, forming an anhydride. This is employed extensively in the preparation of dyes.

172. Mesitylene, symmetrical trimethyl benzene, $C_6H_3(CH_3)_3$, is formed by methods analogous to the formation of xylene (**171**), and also by the polymerization of acetone in the presence of strong sulphuric acid:

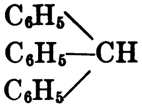


Another class of hydrocarbons is known in which two or three phenyl groups replace as many hydrogen atoms in the methane group:

$C_6H_5—CH_3$
Toluene
or
phenyl methane



Diphenyl methane

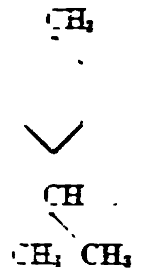


Triphenyl methane

Diphenyl methane is formed by the interaction of benzyl chloride with benzene by the Friedel and Crafts reaction.

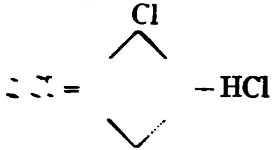
Triphenyl methane is prepared in large quantities in the dye industry from chloroform, $CHCl_3$, and benzene, likewise by the Friedel and Crafts reaction (**169**).

173. Cymene, or methyl-p-isopropyl benzene, occurs



[illegible] is. It yields successively on oxi- [illegible] and teraphthalic acids **171** .

[illegible] Derivatives of Benzene. Chlorine acts upon [illegible] its hydrogen atoms in a manner [illegible] hydrocarbons.



Chlorbenzene

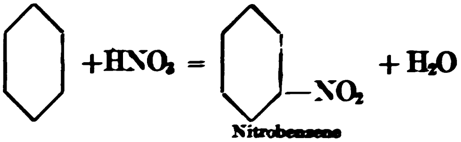
[illegible] accelerated by the presence of [illegible] in part due to the fact that in the [illegible] ICl and ICl_3, the molecule [illegible] up with the formation of *nascent* [illegible] the instability of the chlorides [illegible] them to dissociate into active, [illegible] will be in the system containing [illegible] of the chlorides of iodine to- [illegible] products.

[illegible] acts directly on benzene with the [illegible] hydrobromic acid gas. The action is greatly [illegible] the presence of metallic aluminum.

Benzene is not acted upon directly by iodine, but iodo benzene can be prepared from aniline by the diazo reaction (177).

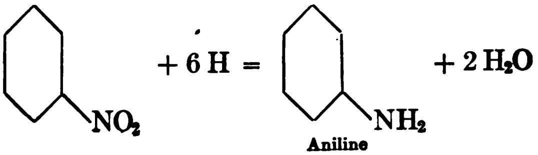
The halogen derivatives of benzene are more stable than the aliphatic halogen compounds. The halogen is not replaceable by other groups, as hydroxyl, etc.

174. Nitrobenzene is produced when concentrated nitric acid acts upon benzene. This action is in marked contrast to the behavior of the aliphatic compounds, which cannot be directly nitrated.



Nitrobenzene is a yellowish oily liquid, which crystallizes when cooled and melts at 3°. It boils without decomposition at 210°. It has the odor of bitter almonds and is employed as a scent for soap. It is but slightly soluble in water, but dissolves in alcohol and ether and in concentrated sulphuric acid. From the latter solution it is precipitated unchanged on dilution with water. Nitrobenzene is prepared on a large scale for the manufacture of aniline.

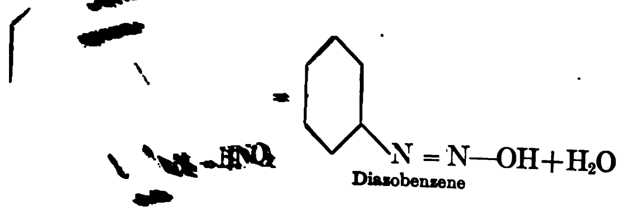
175. Aniline, $C_6H_5NH_2$, *aminobenzene,* results from the action of nascent hydrogen on nitrobenzene:



Aniline may be rega… …line under pressure
The benzene nucle…
moved is termed th… …$H_5)_2 = NH - NH_4Cl$
breviated to C_6H_5-
structure is desired. …egative character of the
phenyl amine. It i… …rogen attached to the
acids. From these… …haves like acid hydrogen
ment with alkalies… …by heating the potassium
and readily so in… …ith brom benzene, there is
istic odor and is…
of central origi…
corpuscles. …$Br = (C_6H_5)_3 \equiv N + KBr$

Triphenyl amine

The presen…
greatly incre… …$N = N$—OH. There is a
atoms can b… …behavior of aniline, a pri-
on benzene… …series, and of the aliphatic
is unumobr… …ormer are converted into the
forming… …while the latter form *diazo*



Diazobenzene

Th…
beha… …from aniline. It behaves like a
par… …is unknown in the free state, since it is so
gro… …it decomposes with an explosion. Its salts
an… …and are safe only in a moist state, since
ta… …violently when struck or heated. The

neans of synthesis f

rmed directly. Th

position to the meth

chlorination of p-tolu-

after be removed by the

r-toluene.

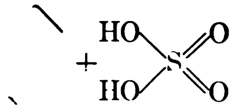
C_6H_5—SO_3H, is formed

lphuric acid on benzene.

which melts at 50°. Its

acid and it forms salts

hydrolyzed into sulphuric



Benzene Sulphuric acid

with alcohols to form esters:

H_5—SO_2—OR + H_2O

igorous reducing agents

$H_5SH + 3 H_2O$

sulphonic acid is replaced

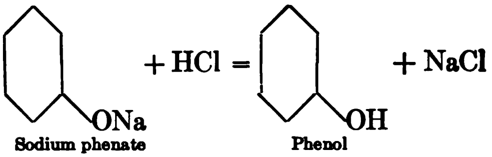
phosphorus pentachloride,

SO_2—Cl + $POCl_3$ + HCl

The salts of benzene sulphonic acid when fused with sodium hydroxide are decomposed into the metallic derivative of phenyl alcohol or *phenol*:

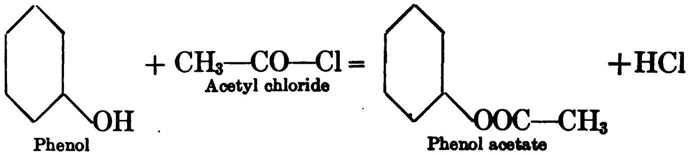
$$C_6H_5—SO_3H + 2\,NaOH = C_6H_5ONa + Na_2SO_3 + H_2O$$

179. Phenol, or *carbolic acid,* is obtained by the action of acids on the sodium phenolate produced by the decomposition of benzene sulphonic acid by fusion with alkalies.

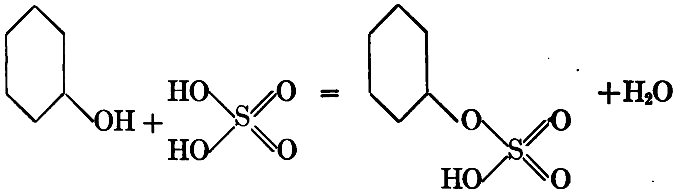


Phenol is present in coal tar and is obtained in the distillation of the latter. It is separated from hydrocarbons and basic compounds by the solubility of its sodium compound in water. Sodium phenolate or phenate is readily formed in aqueous solutions of sodium hydroxide. In this respect phenol shows properties markedly different from the alcohols of the aliphatic series. These are neutral in reaction and form metallic derivatives, the alcoholates, only in non-aqueous solutions and with the alkali metals. Phenol, while chemically a tertiary alcohol, has distinctly acid properties. It is not a sufficiently strong acid to react with carbonates, however, and while, *e.g.*, sodium phenolate is stable to water, it is decomposed by carbon dioxide.

As an alcohol phenol forms esters, but these are not readily formed by the direct heating of phenol with an acid. They are easily formed by the action of acid chlorides upon phenol or its salts:



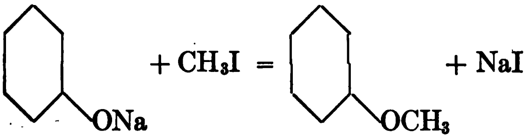
180. Phenol Sulphuric Acid, also called *phenyl sulphuric acid,* is formed in the animal body by the union of phenol with sulphuric acid. Since phenol is a product of the putrefaction of proteins by bacteria in the intestine, it is regularly absorbed to some extent. Phenyl sulphuric acid is therefore a regular constituent of the urine, and its amount depends upon the extent to which putrefaction goes on in the alimentary canal:



or $C_6H_5O—SO_3H$

181. Phenol Sulphonic Acids. On dissolving phenol in concentrated sulphuric acid the sulphonic acid group is readily introduced into the benzene nucleus and *phenol sulphonic acids* are formed. The o- and p- derivatives are thus obtained. When two sulphonyl groups are introduced into benzene they take the meta position and on fusion with potassium hydroxide one is replaced by hydroxyl, forming m-phenol sulphonic acid.

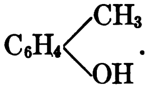
182. Phenol Ethers. Phenol also forms ethers, but not readily by the direct action of phenol with an alcohol. They are easily produced by the action of alkyl iodides upon the phenolates (also called phenates):



Phenol when pure is a colorless crystalline compound which is very deliquescent and turns pink on contact with the light and air. It is volatile with steam, melts at 42°, and boils at 182°. Its specific gravity at 0 is 1.084°. Its odor is characteristic, and it is highly toxic and corrosive, the latter action being due to its great affinity for water. One part of phenol dissolves in fifteen parts of water. It is much more soluble in alcohol. It is an excellent antiseptic.

Phenol can be formed by the direct oxidation of benzene in the presence of palladium black or aluminum chloride.

Like aniline, phenol is readily brominated. When bromine water is added to a solution of phenol, symmetrical tribrom phenol, a very insoluble compound, crystallizes out. This compound has served for the quantitative estimation of phenol. Phenol in water gives a violet coloration on adding a few drops of a solution of ferric chloride.



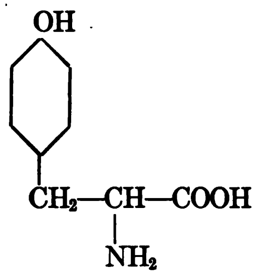
183. Cresols, $C_6H_4\left\langle\begin{matrix}CH_3\\OH\end{matrix}\right.$. There are three homologues of phenol, the o-, m-, and p-, methyl phenols or cresols.

They all occur in the distillate from coal tar. They possess antiseptic properties and are much employed in disinfection. When pure they are crystalline solids. o-cresol melts at 31°, the m- and p-cresols at 5° and 36° respectively. Like phenol they give a coloration with ferric chloride and are readily brominated and nitrated.

184. Picric Acid. Nitric acid acts energetically on phenol, forming symmetrical trinitro phenol, or *picric acid.* The latter compound is also formed by the action of nitric acid upon various substances containing proteins, since the phenyl and phenol groups are contained in two of the amino acids found in nature, viz. phenyl alanine and tyrosine. Picric acid is a bright yellow crystalline substance of strongly acid character. The introduction of negative groups, as halogens, or nitro groups, into phenol increases its acid character, while the introduction of basic groups, as NH_2, depresses the acid character.

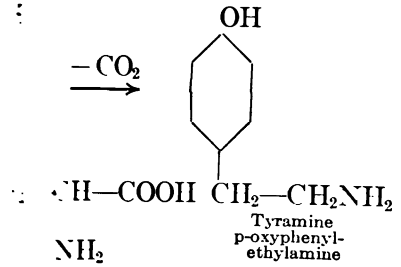
Picric acid forms readily crystallizing salts of slight solubility with many natural bases and is of great importance in the isolation and purification of these. It melts at 122° and can be sublimed without decomposition, but is explosive, owing to the large amount of oxygen contained within its molecule, which makes possible its complete and sudden self-oxidation. The salts of picric acid are much more explosive, decomposing with violence when heated or struck.

185. Tyrosine, α-amino, β-oxyphenyl propionic acid, or *para-oxyphenyl alanine:*



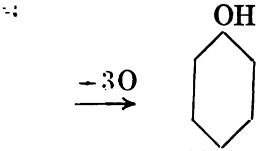
is a constituent of many proteins, and was first isolated by Liebig in 1846. It is set free from its union with other amino acids during the digestion of the proteins, and is also formed by boiling proteins with mineral acids. It is not present in gelatin, and the best yield is obtained from the hydrolysis of silk. With the other amino acids it is always present in the blood in minute amounts. Tyrosine is a colorless compound forming long silky needles which are but slightly soluble in cold water, but more easily in hot. Dilute acids or alkalies dissolve it, and on neutralizing the solutions, it crystallizes out. It gives a red color with a solution of mercuric nitrate in nitric acid, containing some nitrous acid. This is the *Millons* reaction, which has long served as a qualitative test for proteins. Gelatin when pure does not respond to this test. This color reaction is also given by phenol and other phenyl derivatives containing a hydroxyl group attached to the benzene nucleus.

Tyrosine is apparently one of the amino acids which is indispensable from the diet. On being acted upon by anaërobic bacteria the alanine complex is removed and phenol formed. Tyrosine is the source of the phenol n in the intestine. The illustrated by the following:



Tyramine
p-oxyphenyl-
ethylamine

sine
xyphenyl-
acid



Phenol

the power of bacteria group in a manner carboxylase on pyruvic from amino acids as side chains.

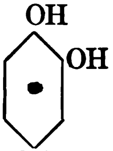
OH:

, or p-oxyphe-

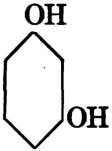
$CH_2—CH_2—NH_2$

a substance of mild toxicity occurring mixtures. Doses of 1-2 mg. injected intravenously cause a sudden and pronounced rise in blood pressure which soon passes away. The absorption of this compound from the intestine is possibly in part responsible for high blood pressure in certain individuals.

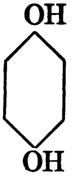
187. Dihydroxy Benzenes.—The three dihydroxy benzenes occur among natural products:



Ortho-
Pyrocatechin
or catechol

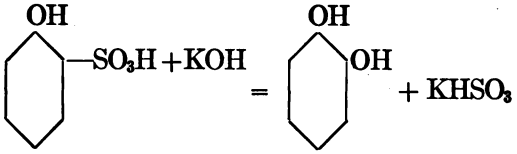


Meta-
Resorcinol



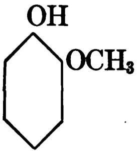
Para-
Hydroquinone or quinol

188. Pyrocatechin, o-dihydroxy benzene, $C_6H_4(OH)_2$, is obtained by fusing o-phenol sulphonic acid with potassium hydroxide:

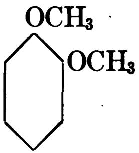


It is a colorless crystalline compound melting at 104°. It occurs in the resin *catechu* and in beech wood tar.

189. Guiacol and **Veratrol** are the monomethyl and the dimethyl ethers respectively of pyrocatechin.



Guiacol



Veratrol

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$C_6H_4(OH$
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lling substance,
le in hot water
ted into hydro-
s golden yellow

TRIHYDROXY BENZENES

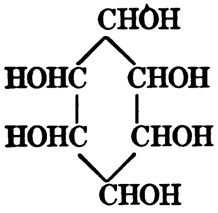
193. **Pyrogallol**: 1, 2, 3 *trihydroxy benzene*, $C_6H_3(OH)_3$, is formed by the distillation of gallic acid (**212**).

$$C_6H_2(OH)_3—COOH = C_6H_3(OH)_3 + CO_2$$

Its alkali salts absorb oxygen readily, and its solution in sodium hydroxide is employed in gas analysis for this purpose. The compound is oxidized and carbon monoxide is liberated as one of the decomposition products. It is employed as a developer in photography.

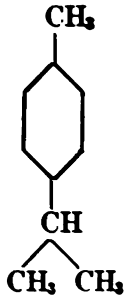
194. **Phloroglucin**, 1, 3, 5 *trihydroxy benzene*, $C_6H_3(OH)_3$, is prepared by the oxidation of resorcinol. It crystallizes from water, and melts at 217°. It gives a blue violet color with ferric chloride.

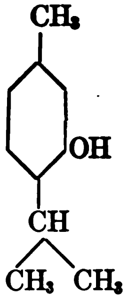
195. **Inosite**, $C_6H_{12}O_6$, occurs in nature in several isomeric forms. It is a derivative of the reduced benzene ring, hexamethylene, and is hexahydroxy benzene:

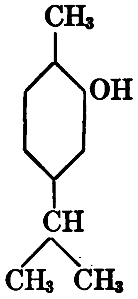


Inosite is found in heart muscle, in the brain, and is widely distributed in plants, especially in beans and peas in the unripe state. Its hexaphosphoric acid ester is called phytic acid, and is present in considerable amount in wheat bran and is a common constituent of plants.

196. Thymol and **Carvacrol** are naturally occurring *methyl-isopropyl phenols*. They are derivatives of cymene.


Cymene

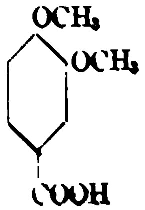

Thymol

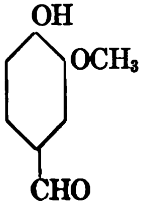

Carvacrol

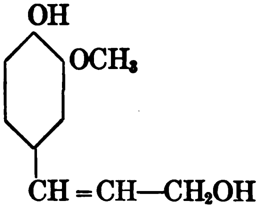
Thymol and carvacrol are found in many plants. They have a very pleasant mint-like odor and possess mild antiseptic action.

197. Protocatechuic Acid, *catechol carboxylic acid*, results from the fusion of many resins with alkali. It is readily soluble in water and melts at 199°.

198. Veratric Acid, Vanillin, and Coniferyl Alcohol. —


Veratric acid

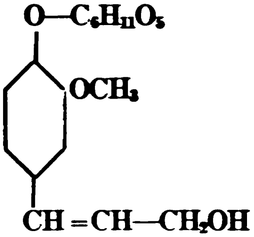

Vanillin


Coniferyl alcohol

Veratric acid, the dimethyl ester of protocatechuic acid, occurs in the seeds of *Veratrum* Sabadilla.

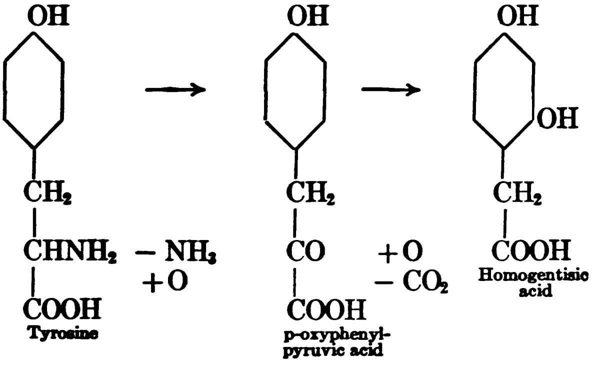
Vanillin is the substance giving the pleasant odor to the vanilla bean. It is obtained by the oxidation of coniferyl alcohol.

Coniferyl alcohol occurs in coniferin, a glucoside found in the cambium sap of all coniferæ and in other plants.



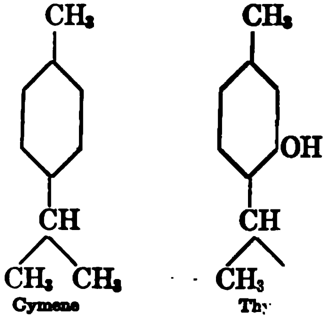
Coniferin (glucoside)

199. **Homogentisic**, *quinol acetic acid*, is a constituent of the urine in a type of abnormal metabolism known as alkaptonuria. The normal animal body is capable of the complete oxidation of the benzene ring when it is introduced in the form of tyrosine or phenyl alanine, but there is an anomaly of metabolism in which the later steps in the process fail. The mode of formation of homogentisic acid from tyrosine is probably as follows:



196. Thymol and Carvacrol are natu

methyl-isopropyl phenols. They are deriv



Cymene Th

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Thymol and carvacr
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197. Protocatechui
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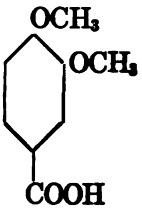
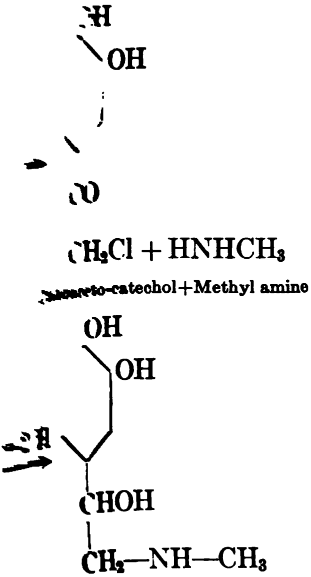
198. Veratric A



Veratric acid



$CH_2Cl + HNHCH_3$

o-catechol+Methyl amine

Adrenin

Veratric
occurs in t
Vanilli

etic product is optically inactive, but has ved into its optical components. The natural levorotatory and greatly surpasses the dextro physiological activity. Adrenin produces a rise of blood pressure through a constriction of d vessels.

Benzoic Acid, C_6H_5COOH, is formed by the oxi- tion of toluol and its homologues containing longer ide chains. It is found in gum benzoin, and other resins. In gum benzoin it is present chiefly as its ester, with benzyl alcohol as benzoate. It occurs also in cranberries.

Benzoic acid is formed from benzotrichloride by boiling with water. The behavior of the three chlor toluenes in which the chlorine is in the side chain, when boiled with water, is of synthetic interest:

$$\underset{\text{Benzyl chloride}}{C_6H_5—CH_2Cl} + HOH = \underset{\text{Benzyl alcohol}}{C_6H_5—CH_2OH} + HCl$$

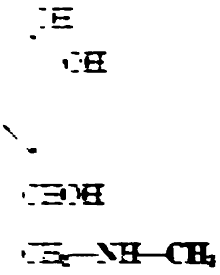
$$\underset{\text{Benzal chloride}}{C_6H_5—CHCl_2} + 2\,HOH = \underset{\text{Benzaldehyde}}{C_6H_5—CHO} + 2\,HCl$$

$$\underset{\text{Benzotrichloride}}{C_6H_5—CCl_3} + 3\,HOH = \underset{\text{Benzoic acid}}{C_6H_5—COOH} + 3\,HCl$$

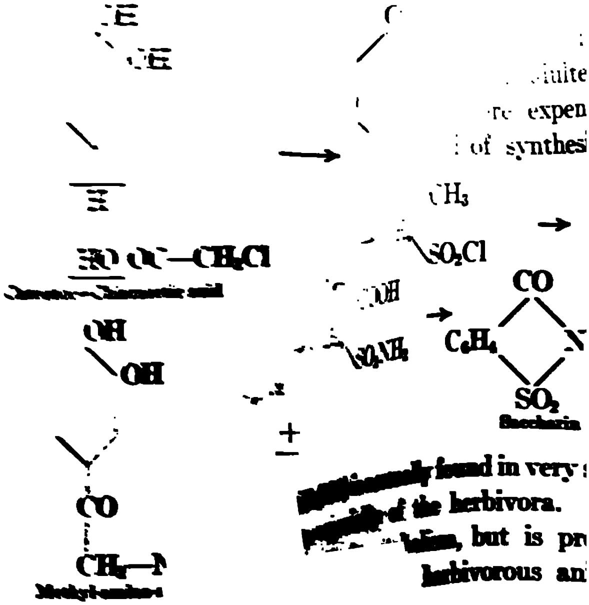
Benzoic acid results from the oxidation of either benzaldehyde or of benzyl alcohol with benzaldehyde as an intermediate product. The acid can also be formed by the hydrolysis of phenyl nitrile (**177**).

Benzoic acid has all the ordinary properties of an acid, forming salts, esters, etc. It is a colorless crystalline compound which is fairly readily soluble in hot water, but very slightly soluble in cold (1 part in 400).

[illegible] Adrenalin.



is the active principle of the adrenal [illegible] the endogenous hormones [illegible] chem[illegible] metabolism. It has been produced [illegible] following reactions.



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herbivorous an

On warming an alcholic solution of benzaldehyde with potassium cyanide two molecules condense to form the ketone alcohol *benzoin.* Benzaldehyde yields nitro derivatives, sulphonic acids, etc. o-nitrobenzaldehyde condenses with acetone to form indigo blue.

PHENYL FATTY ACIDS

[illegible] **Phenyl Acetic Acid** is formed in small amounts in putrefaction of proteins. It is closely related to mandelic acid, the nitrile of which occurs in amygdalin:

$$C_6H_5CH_2—COOH \qquad C_6H_5CHOH—COOH$$

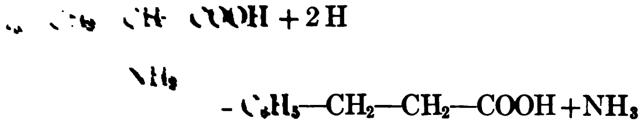
Phenyl acetic acid — Mandelic acid

Its nitrile is formed from benzyl chloride by the action of potassium cyanide:

$$C_6H_5CH_2Cl + KCN = C_6H_5CH_2CN + KCl$$

[illegible] **Phenyl Amino Propionic Acid,** $C_6H_5—CH_2—CH(NH_2)—COOH$, or *phenyl alanine,* is a constant constituent [illegible]

[illegible] On putrefaction it gives rise to phenyl propionic acid:



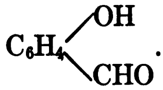
$$C_6H_5—CH_2—\underset{NH_2}{CH}—COOH + 2H = C_6H_5—CH_2—CH_2—COOH + NH_3$$

Phenyl alanine is not readily isolated from among the [illegible] hydrolysis of proteins. The form which [illegible] is laevorotatory. It is crystalline and [illegible]

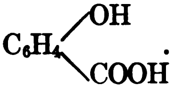
207. Cinnamic Acid, $C_6H_5\text{—CH}=\text{CH—COOH}$, phenyl acrylic acid, is found in the resin storax. It is the most important phenyl derivative containing an unsaturated side chain. A synthesis described by Perkin is of unusual interest. Benzaldehyde condenses with sodium acetate when the two are heated together in the presence of a dehydrating agent (acetic anhydride).

$$\underset{\text{Benzaldehyde}}{C_6H_5\text{—CH}}\boxed{O + H_2}\underset{\text{Sodium acetate}}{\text{CH—COONa}} = C_6H_5\text{—CH}=\text{CH—COONa}$$

Alcohol, aldehyde and acid derivatives of phenol are also found in nature. The first of these is represented by saligenin, which occurs in the glucoside *salicin* in willow bark. It is a crystalline solid easily soluble in water and melting at 82°. The phenol group is in the ortho position.

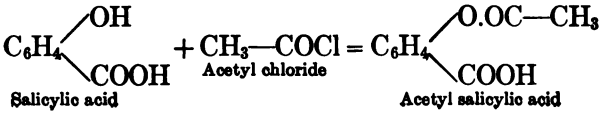


208. Salicylic Aldehyde, $C_6H_4\begin{smallmatrix}\diagup OH\\ \diagdown CHO\end{smallmatrix}$. The ortho-compound is found in certain volatile oils.



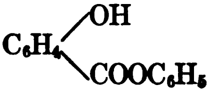
209. Salicylic Acids.—$C_6H_4\begin{smallmatrix}\diagup OH\\ \diagdown COOH\end{smallmatrix}$. The ortho- compound is of greatest importance. It occurs as the methyl ester in oil of wintergreen, and the acid is likewise found in the flowers of Spiræa.

210. Aspirin is acetyl salicylic acid:

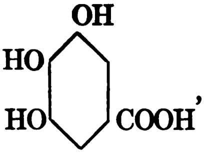


$$\underset{\text{Salicylic acid}}{C_6H_4\begin{smallmatrix}\diagup OH\\ \diagdown COOH\end{smallmatrix}} + \underset{\text{Acetyl chloride}}{CH_3\text{—COCl}} = \underset{\text{Acetyl salicylic acid}}{C_6H_4\begin{smallmatrix}\diagup O.OC\text{—}CH_3\\ \diagdown COOH\end{smallmatrix}}$$

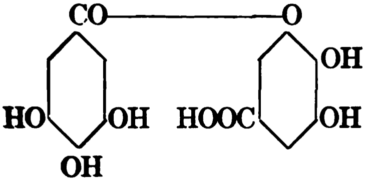
211. Salol is phenyl salicylate:



$$C_6H_4\begin{cases}OH\\COOC_6H_5\end{cases}$$

212. Gallic Acid,  , is found in many plants, as gall nuts, tea, etc. It is formed when tannin is hydrolyzed. It is a crystalline compound melting at 220°. It gives the same reaction with ferric chloride as does pyrogallol.

213. Tannic Acid, or *digallic acid,*

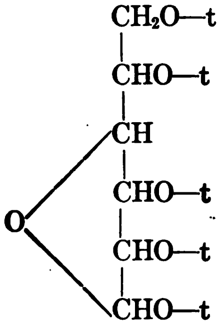


Tannic acid

is an ester formed between two molecules of gallic acid. It occurs in gall nuts, sumach, and other barks.

214. Tannins are of several varieties, distinguished by the color reactions which they give with various reagents. There are distinguished two general classes, the pyrogallol and the catechol varieties. The former give a dark blue color with ferric salts (ink) and the latter a greenish black. The latter forms a dark red ring at the juncture of the liquids when its solutions are treated with concentrated sulphuric acid.

Tannin on hydrolysis yields 7–8 per cent of glucose, and gallic acid. Its constitution has not been determined with certainty, but it is in some samples the penta digallic ester of glucose:

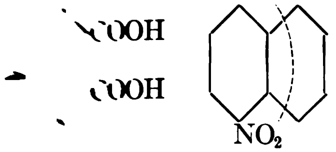


t represents digallic or tannic acid in this formula. One of the tannins recently synthesized by Fischer has nearly double the molecular weight of the most highly complex compound hitherto synthesized.

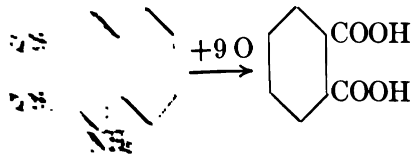
XVIII

...ZENE RINGS

... s present in considerable ...ucture is made clear by the ...ino derivatives on oxidation. ...ields phthalic acid (**171**), ...s a benzene nucleus and two ... ho position. On oxidizing ...alic acid is formed. When ... an amino group and the ...halic acid is formed. The ... of two benzene rings hav- ...on:



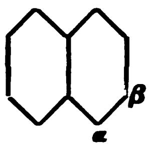
...thalic acid Nitronaphthalene



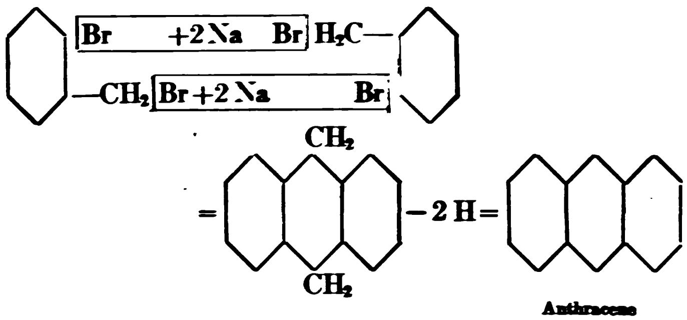
...mino naphthalene Phthalic acid

Naphthalene derivatives are extensively employed in the manufacture of dyes.

Naphthalene yields two mono substitution products α- and β-:



216. Anthracene, $C_{14}H_{10}$, is formed by the Fittig synthesis from α-brom benzyl bromide, with subsequent oxidation:



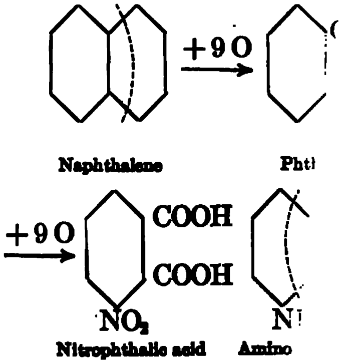
The structure of an anthracene derivative is arrived at through a study of the structure of its simpler oxidation products.

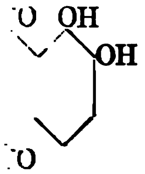
Anthracene is a constituent of coal tar, and is the mother substance of the red dye derived from the madder root. It is a colorless crystalline solid with a blue fluorescence, which melts at 213° and boils at 351°. It is easily soluble in benzene but difficultly in water, alcohol, and ether.

CHAPTER XVIII

CONDENSED BENZENE

215. Naphthalene, $C_{10}H_8$, is preser
amount in coal tar. Its structure is
behavior of its nitro and amino deriv
Naphthalene on oxidation yields
which shows that it contains a ben
substituting groups in the ortho p
the nitro compound, nitrophthalic
the nitro group is reduced to a
naphthyl amine oxidized, phthal
molecule must therefore consist
ing two carbon atoms in commo



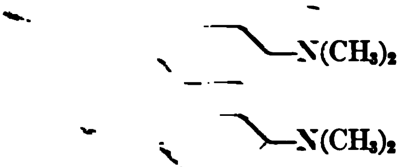


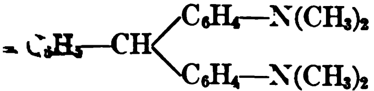
Isopurpurin

[illegible] derivatives of anthracene containing [illegible] position to each other are dyes.

TRIPHENYL METHANE DYES

[illegible] is formed by heating benzaldehyde [illegible] aniline and a dehydrating agent





$$= C_6H_5—CH\begin{cases}C_6H_4—N(CH_3)_2\\C_6H_4—N(CH_3)_2\end{cases}$$

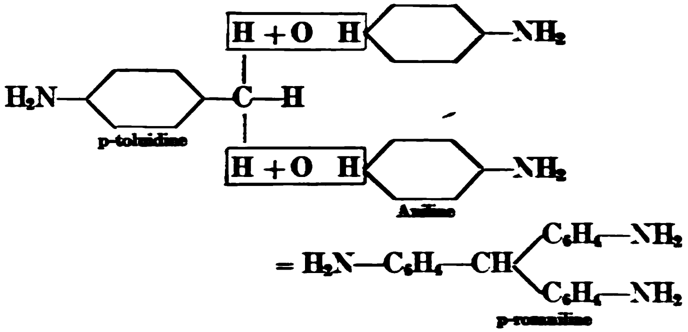
Leuco base of malachite green

[illegible] silk and wool, but for dyeing [illegible]

[illegible] in the same way as is mala[redacted]employed.

malachite green except

p-toluidine and aniline

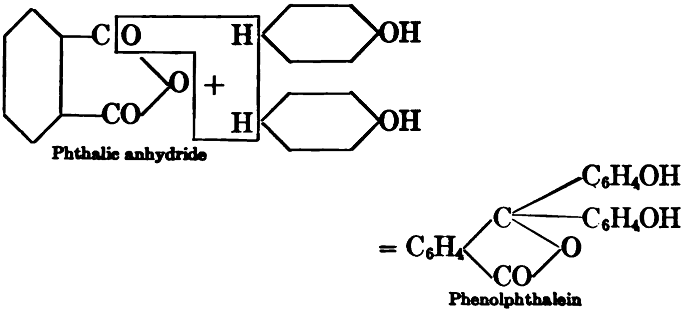


Rosaniline, ***fuchsine,*** **or** ***magenta,*** is prepared from a mixture of p-toluidine, o-toluidine, and aniline in an analogous manner.

Rosaniline and pararosaniline are reddish-blue dyes and can be converted into dyes having a bluer tint by methylation with methyl iodide (176).

Ethylation of the amino groups forms deeper blue dyes, while phenylation forms a pure blue dye known as *aniline blue.*

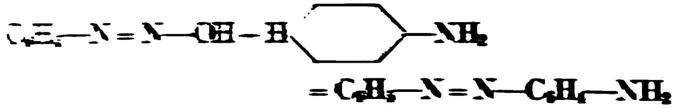
Phenolphthalein is another triphenyl methane derivative formed from phenol and phthalic anhydride:



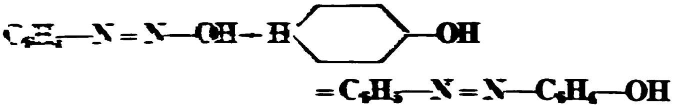
Fluorescein, eosin, erythrosin, and many other dyes are derivatives of triphenyl methane.

THE AZO DYES

[illegible] By substituting the hydroxyl of diazo-benzene (277) by amines, phenols, etc., a great number of dyes of both basic (from amines) and acid (from phenols) character have been produced:



$$C_6H_5—N=N—OH + H\langle\;\rangle—NH_2 = C_6H_5—N=N—C_6H_4—NH_2$$



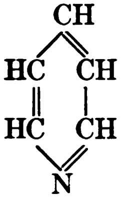
$$C_6H_5—N=N—OH + H\langle\;\rangle—OH = C_6H_5—N=N—C_6H_4—OH$$

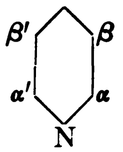
Congo red, bismarck brown, chrysoidin, helianthin, resorcin yellow, belong to this class.

CHAPTER XX

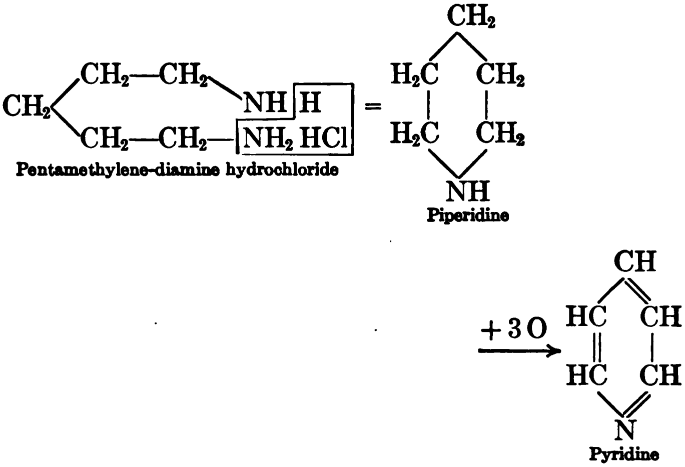
HETEROCYCLIC COMPOUNDS

220. Pyrrole, pyrimidines, and imidazoles have been already described as representing compounds of cyclic structure in which both carbon and nitrogen were present. It remains to describe the six-membered ring containing five carbon atoms and one nitrogen. The simplest member of this group is pyridine. Neither pyridine nor its derivatives play a rôle in the biological processes of animal life as do the heterocyclic compounds mentioned above, but it is found widely distributed in plants, especially in the alkaloids. Pyridine itself is a highly toxic substance. It is represented as follows:





Its structure is arrived at by a method for its formation. Pentamethylene diamine (74) hydrochloride on dry distillation loses a molecule of ammonium chloride with the formation of the reduced cyclic structure *piperidine* which on oxidation yields pyridine:

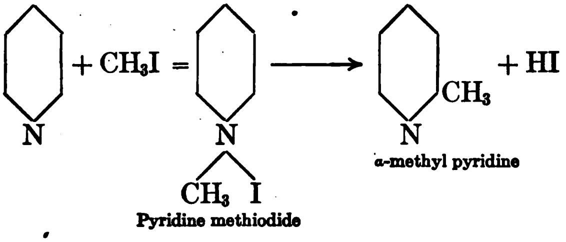


Pyridine and certain of its homologues are present in coal tar, and in "Dippel's Oil," the foul-smelling product of the dry distillation of bones.

Pyridine is a colorless liquid with the odor of tobacco smoke. It is a strongly alkaline substance which mixes with water in all proportions. It boils at 115°. It is one of the most stable of organic substances, being unattacked by boiling nitric or chromic acid. With sulphuric acid it reacts, forming a sulphonic acid. Halogens scarcely attack it. On heating pyridine with hydriodic acid at 300° it is destroyed, yielding normal pentane and ammonia.

Pyridine forms salts with acids. It does not form a nitroso derivative with nitrous acid.

As a tertiary amine pyridine combines with alkyl halides. These show an interesting rearrangement when heated, the alkyl group changing its position from the nitrogen to the α-carbon atom.



A delicate test for pyridine consists in heating the substance to be tested with a few drops of methyl iodide, then adding a small quantity of solid potassium hydroxide and heating again. Methyl pyridine hydroxide, having an extremely disagreeable odor, is formed when pyridine is present.

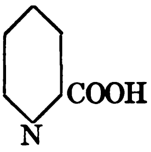
Piperidine, $C_5H_{10}NH$, is formed by heating the hydrochloride of pentamethylene diamine (**74**) or by the reduction of pyridine with sodium and alcohol. It behaves like a secondary amine in forming a nitroso derivative when treated with nitrous acid.

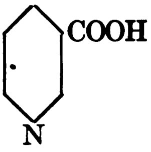
Piperidine occurs as a constituent of the alkaloid piperine found in pepper. It is a strong base, which boils at 106°.

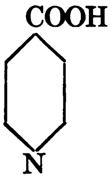
HOMOLOGUES OF PYRIDINE

The methyl pyridines are known as *picolines;* the dimethyl pyridines, as *lutidines;* and the trimethyl pyridines, as *collidines.* Their properties are closely similar to those of pyridine.

221. Nicotinic Acid is the β-pyridine carboxylic acid:


Picolinic acid

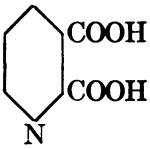

Nicotinic acid


Isonicotinic acid

Nicotinic acid is derived from the alkaloid nicotine by oxidation.

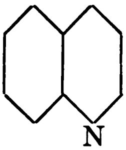
Picolinic acid is distinguished from the other isomeric acids by its property of giving a red color with ferrous sulphate.

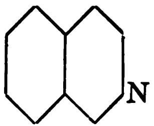
Quinolinic Acid is an α-β-dicarboxy pyridine. At 190°


Quinolinic acid

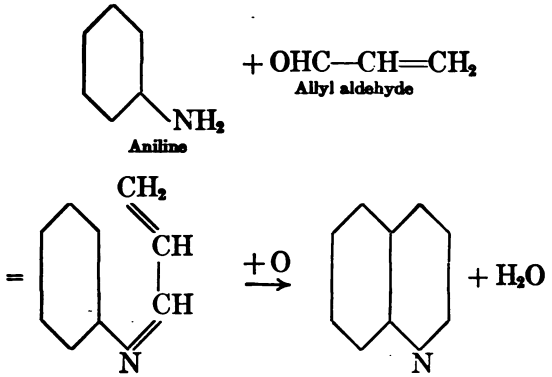
it loses carbon dioxide and is converted into nicotinic acid.

222. Quinoline is a compound containing a benzene ring condensed with a pyridine ring:

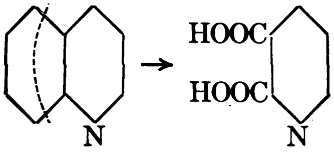

Quinoline


Isoquinoline

Both isomers occur in coal tar, but quinoline is usually prepared by synthesis. Its structure is made clear by its synthesis from allyl aniline by oxidation:



and further by the fact that quinoline yields on oxidation quinolinic acid:



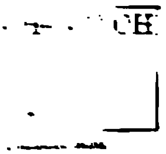
It is a colorless liquid of an oily consistency which boils at 239° and has a characteristic rather pleasant smell.

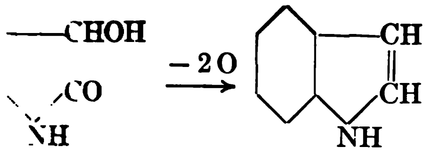
Isoquinoline closely resembles quinoline, but is a solid which melts at 23° and boils at 241°.

Both quinoline and isoquinoline are constituents of alkaloids.

INDOLE AND ITS DERIVATIVES

223. Indole is a compound which contains a condensed benzene and a pyrole ring, the two having two ortho- carbon atoms in common. It is found in coal tar and is a constituent of one of the important amino acids contained [illegible] mandelic acid is converted by the [illegible] dioxindole, from which by vigor- [illegible] formed:

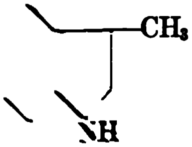




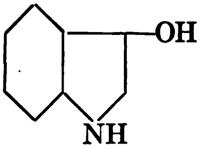
[illegible] and melts at 52°. It has a fecal-like [illegible] with steam. It is soluble in various [illegible]

[illegible] which gives the red color with sul- [illegible] acid (Hopkins and Cole's re- [illegible] teristic of many proteins.

[illegible] **Skatole**, is found in putrefaction [illegible] where it results from tryptophane, [illegible]

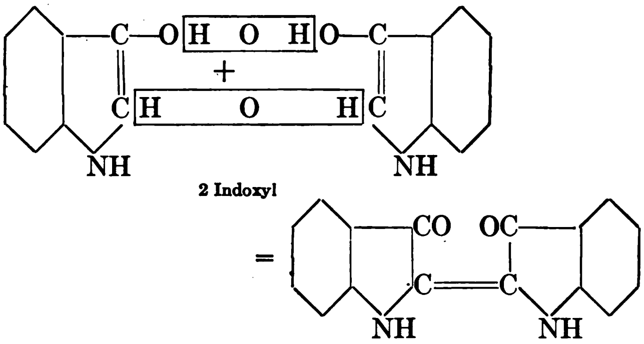


[illegible] in Isatis tinctoria as a glucoside,



This is hydrolyzed by an· enzyme in the plant and the free indoxyl undergoes oxidation to the blue dye *indigo.* Indoxyl is a product of the putrefaction of tryptophane and is formed in the intestine from proteins and being absorbed is eliminated in the urine, principally as indoxyl sulphuric acid, which is analogous to phenol sulphuric acid (**180**) in its constitution. The formation of indigo is the basis of the *indican* reaction of urine.

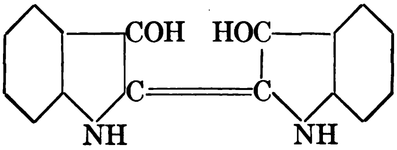
226. Indigo:



2 Indoxyl

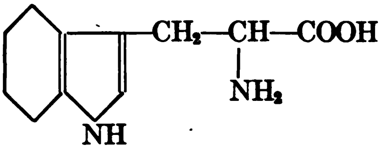
Indigo blue

Indigo white is a reduction product of indigo blue:



Indigo white

227. **Tryptophane,** or α-amino, β-indole propionic acid, is



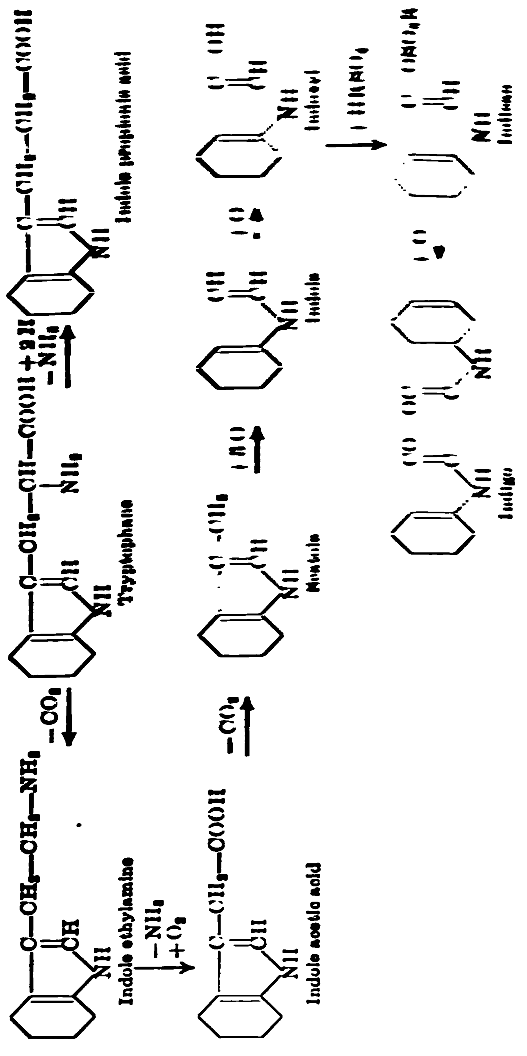
a constituent of many proteins. It is the complex which gives Adamkiewic's reaction for proteins (Hopkins-Cole reaction).

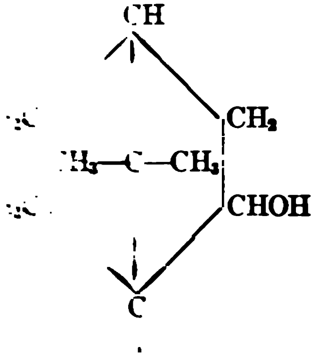
It is a colorless crystalline compound readily soluble in hot water, but difficultly soluble in cold. Insoluble in absolute alcohol and in ether. It is soluble in hot pyridine. It melts at 252° after becoming brown at 240°. It is a weak base and forms salts with acids. Some of its acyl derivatives formed by the action of acid chlorides are of experimental value because of their properties. Tryptophane is destroyed in the hydrolysis of proteins by mineral acids, but is stable to barium hydrate.

Tryptophane gives a red color when a trace of bromine is added to its solutions acid with acetic acid. With concentrated sulphuric acid and glyoxylic acid it gives a reddish violet color.

Persons suffering from melanotic tumor excrete a pigmented substance called melanin in the urine. It has been rendered highly probable that the tryptophane complex in the protein molecule is the chief precursor of melanin in such subjects.

The more important products resulting from tryptophane in biological processes are represented by the following transformations:


C—CH₂—CH₂—NH₂
CH
NH
Indole ethylamine
−CO₂
C—CH₂—CH—COOH + 2H
NH₂
Tryptophane
−NH₃
C—CH₂—CH₂—COOH
Indole propionic acid
−NH₃
+O₂
C—CH₂—COOH
Indole acetic acid
−CO₂
C—CH₃
Skatole
Indole
Indoxyl
Indican
Indigo

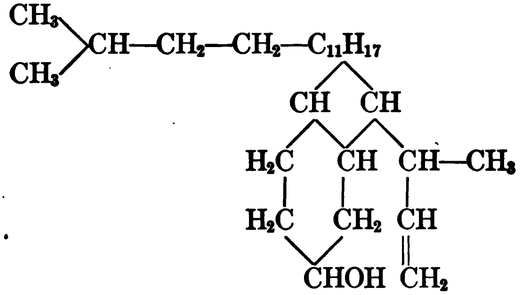


Borneol

[illegible] skeleton illustrated and a union between [illegible] pinene consists of a six-membered [illegible] ring. *Borneol* is believed to have a [illegible] giving the formula shown above. [illegible] chief constituent of turpentine from [illegible] Greece, while that from France and [illegible] borneol is found in the product from [illegible]

[illegible]terpene from the camphor tree. It [illegible] by oxidation. It differs from [illegible] ketone group.

[illegible] are closely related to the ter- [illegible] the hard fats in their phys- [illegible] from these in their remarkable [illegible] Micro-organisms do not [illegible] appear to be formed in every cell [illegible] and they play an important rôle [illegible] by reason of their peculiar physical properties. The structure of cholesterol is not entirely known, but Windaus assigns to it the following partial provisional constitution:



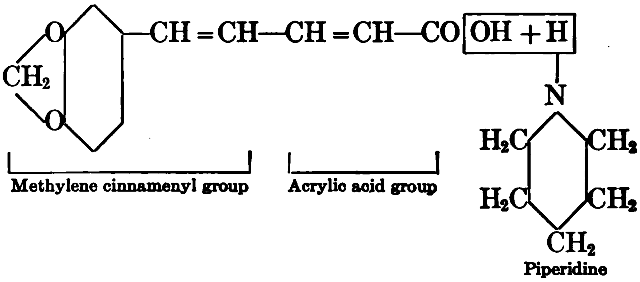
The nature of the complex $C_{11}H_{17}$ is entirely unknown. The properties of cholesterol have already been described (**99**).

CHAPTER XXII

THE ALKALOIDS

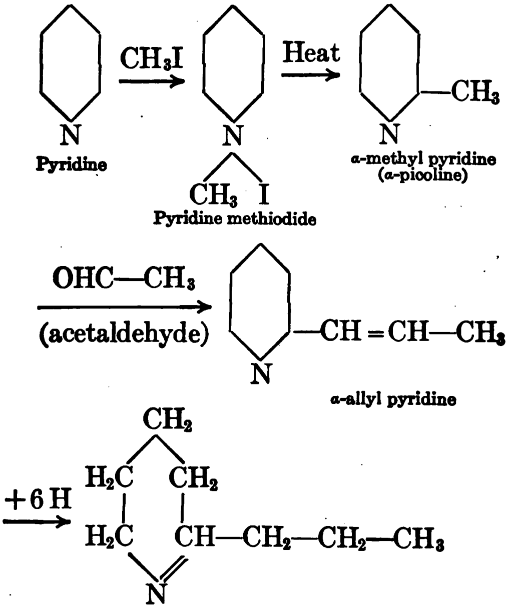
The term alkaloid now includes those basic substances occurring in plants which are derived from pyridine, quinoline, isoquinoline, tropaine, or pyrrolidine.

230. Piperine, $C_{17}H_{19}NO_3$, is a derivative of pyridine. On hydrolysis it yields piperidine and an acid, *piperic acid*, which may be regarded as the methylene ester of cinnamenylacrylic acid:



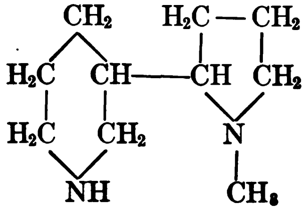
Piperine is a white solid substance melting at 128°. It does not dissolve in water, but is soluble in alcohol and ether. Black pepper contains about 8 per cent of this alkaloid.

231. Coniine, $C_8H_{17}N$, is the poisonous principle of the hemlock. It is dextrorotatory α-n-propylpiperidine. It is a strong base which distills with steam when the seeds of hemlock are distilled with sodium hydroxide. It was the first of the alkaloids to be synthesized. The steps by which Ladenburg accomplished this are as follows:



α-propyl-piperidine (coniine)

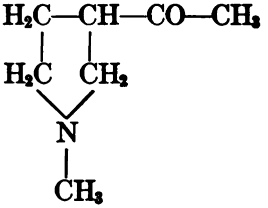
232. Nicotine, $C_{10}H_{14}N_3$, contains both a piperidine and a pyrrolidine ring. It is a colorless oily substance which



boils at 247° and has an unpleasant smell and an extremely burning taste. Naturally occurring nicotine is levorotatory. The synthetic product is inactive, and d-nicotine has been prepared from it and from the natural product after racemization. The physiological effects of the natural form are twice as pronounced as are those of the optical isomer d-nicotine. It is extremely poisonous.

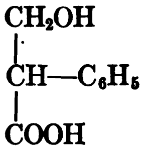
The alkaloids are not found generally distributed in plants, but certain ones are produced only by particular plant groups. The formation of pyrrolidine from tetramethylene diamine (**117**) and piperidine from pentamethylene diamine (**320**) give a clue to their mode of formation in the metabolism of the plant. These are formed from ornithine and lysine respectively, both of which amino acids occur in the course of protein decomposition. The formation of alkaloids is doubtless closely associated with the protein metabolism of the plant.

233. Hygrine, an alkaloid found in coca leaves, is β-acetyl-N-methyl pyrrolidine:



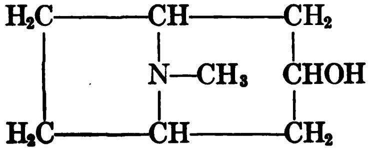
234. Atropine and Hyoscyamine differ chemically only in respect to their optical properties, the former being the d, l- and the latter the l-hyoscyamine. Atropine is found in the deadly nightshade and in henbane, and hyoscyamine in the Jamestown weed, *Datura stramonium.* It is a white crystalline substance melting at 115°, readily soluble in alcohol, ether, and chloroform, but sparingly soluble in water. It is one of the most poisonous substances known.

On hydrolysis atropine yields tropic acid and tropine. Tropic acid has been shown to be α-phenyl-β-hydroxy propionic acid:

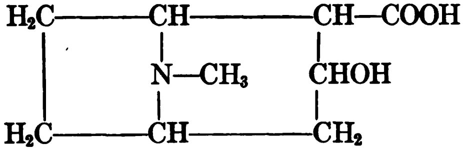


$$\begin{array}{l} CH_2OH \\ | \\ CH{-}C_6H_5 \\ | \\ COOH \end{array}$$

Tropine is made up of two condensed rings, one with five members, the other with six, a nitrogen atom serving as a " bridge."



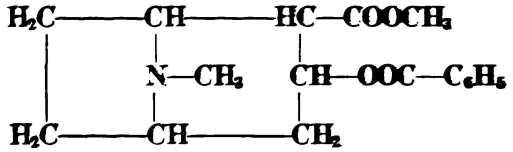
Tropine



Ecgonine

Atropine is the ester of tropic acid with the secondary alcohol tropine.

235. Cocaine, $C_{17}H_{21}NO_4$, is an alkaloid in coca leaves. It is crystalline and melts at 98°. On hydrolysis it yields methyl alcohol, benzoic acid, and ecgonine. Its formula is:



236. Cinchonine, $C_{19}H_{22}N_2O$, present with *quinine* in cinchona bark, yields cinchonic acid or quinoline carboxylic acid and a piperidine derivative.

The structure of quinine is similar but is not known with certainty. It yields both quinoline and pyridine derivatives on hydrolysis.

237. Strychnine, $C_{21}H_{22}N_2O_2$; **Brucine,** $C_{23}H_{26}N_2O_4$, and **Curarine** are all present in the seeds of *Strychnos nux vomica* and other plants of that family. They are all extremely poisonous. Strychnine yields both quinoline and indol on fusion with alkalies. The constitution of these alkaloids is not known.

238. Morphine, $C_{17}H_{19}NO_3$, occurs in the juice of the poppy. There are a number of other alkaloids in the plant. Opium is the dried juice of the seed capsule of *Papaver somniferum,* a variety of poppy. It contains other alkaloids as well as a large number of substances such as fats, resins, proteins, sugars, inorganic salts, etc.

239. Papaverine, Narcotine, Narceine, Laudanosine, are all found in opium along with morphine. They are derivatives of isoquinoline.

CHAPTER XXIII

ORGANIC ARSENIC COMPOUNDS

240. Cacodylic acid, $(CH_3)_2AsO—OH$. This organic arsenic derivative is formed when potassium acetate is distilled with arsenic trioxide. The principal reaction is represented by the following equation:

$$As_2O_3 + 4\,CH_3—COOK$$
$$= \underbrace{(CH_3)_2{=}As—O—As{=}(CH_3)_2}_{\text{Cacodyl oxide}} + 2\,K_2CO_3 + 2\,CO_2$$

The distillate is an oily liquid with an overpowering odor and extremely poisonous properties. The radical $—As(CH_3)_2$ corresponds to $—N(CH_3)_2$. In the distillate is also a substance called cacodyl:

$$\underbrace{(CH_3)_2{=}As—As{=}(CH_3)_2}_{\text{Cacodyl}}$$

Cacodyl and its homologues are analogous to the substituted hydrazines $R_2{=}N—N{=}R_2$.

Cacodyl oxide when treated with hydrochloric acid yields cacodyl chloride:

$$(CH_3)_2{=}As—O—As{=}(CH_3)_2 + HCl = 2(CH_3)_2As—Cl$$

Both cacodyl and cacodyl oxide are converted into cacodylic acid by oxidation. The most important salt is the sodium salt, which has been much used in medicine. It corresponds to the formula

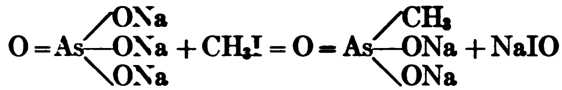
$$(CH_3)_2AsO—ONa + 3\,H_2O$$

This salt is a white crystalline powder which dissolves readily in water. It is much less poisonous than are the salts of arsenious acid.

241. Arrhenal, sodium methyl arsenate,

$$CH_3\text{—}AsO(ONa)_2,$$

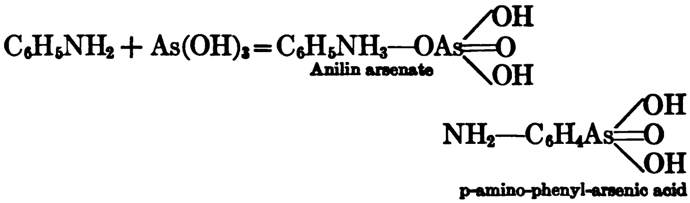
is formed by the action of methyl iodide on sodium arsenate in alkaline solution:



$$O=As\begin{matrix}\diagup ONa\\ \text{—}ONa\\ \diagdown ONa\end{matrix} + CH_3I = O = As\begin{matrix}\diagup CH_3\\ \text{—}ONa\\ \diagdown ONa\end{matrix} + NaIO$$

The great stability of these arsenic derivatives containing aliphatic radicals, and the correspondingly slight arsenical effect which follows their administration, has led to the substitution in great measure of aromatic arsenic compounds in medicine.

242. Atoxyl, *sodium p-amino-phenyl-arsenate*, is formed when aniline and arsenic acid are heated together. As an intermediate product, aniline arsenate, is formed:

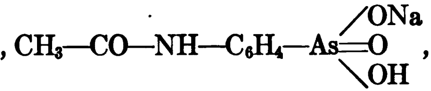


$$C_6H_5NH_2 + As(OH)_3 = C_6H_5NH_3\text{—}OAs\begin{matrix}\diagup OH\\ =O\\ \diagdown OH\end{matrix}$$

Anilin arsenate

$$NH_2\text{—}C_6H_4As\begin{matrix}\diagup OH\\ =O\\ \diagdown OH\end{matrix}$$

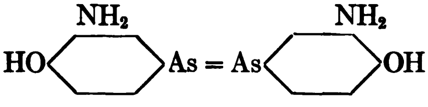
p-amino-phenyl-arsenic acid



Acetylatoxyl, $CH_3\text{—}CO\text{—}NH\text{—}C_6H_4\text{—}As\begin{matrix}\diagup ONa\\ =O\\ \diagdown OH\end{matrix}$, is also employed as a compound for the slow administration of arsenic in medicine.

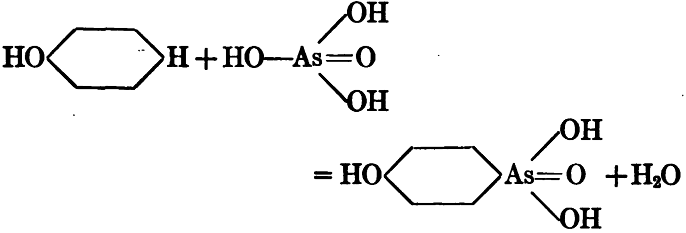
Acetyl atoxyl

Salvarsan, an arsenic compound having a peculiar specific toxic effect upon the protozoa causing syphilis, is one of the most valuble remedies yet discovered. It is p-dihydroxy-m-diamino-arseno-benzene. The following reactions illustrate its preparation:



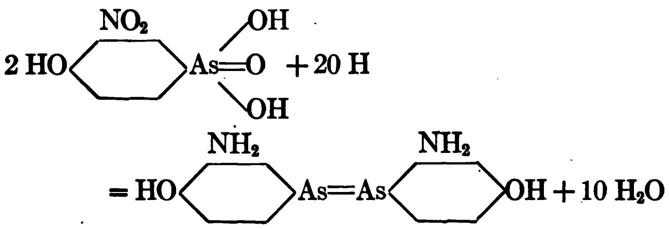
p-dihydroxy-m-diamino-arseno-benzene

On heating phenol with arsenic acid, condensation takes place at the para position:



p-phenol arsenic acid

On nitration this yields a nitro derivative having the —NO_2 group in the o- position to the —OH. On complete reduction of this compound the nitro group is converted into an amino group and the oxygen is removed from the arsenic acid group, the two residues are condensed:



Salvarsan is a derivative of arseno-benzene,

$$C_6H_5—As=As—C_6H_5$$

which is analogous to azo benzene: $C_6H_5—N=N—C_6H_5$.

CHAPTER XXIV

THE PROTEINS

243. The proteins form a very important group of substances which constitute the greater part of the solids of animal tissues and are present in all tissues of both animal and plant origin. The white of egg, silk, hair, nails, and casein, the part of milk which is separated in curdling, are typical examples of proteins.

Chemically the proteins are made up of amino acids; seventeen of these, glycocoll, alanine, valine, leucine and isoleucine, phenylalanine, tyrosine, serine, cystine, proline, oxyproline, aspartic acid, glutaminic acid, arginine, lysine, histidine, and tryptophane have been isolated and identified. These have all been described in this book. It is possible that there are others as yet unidentified.

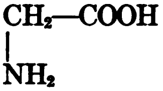
The proteins differ most widely in their physical properties, some being soluble in water (albumins), others insoluble in water, but soluble in dilute salt solutions (globulins), others insoluble in both these solvents, but soluble in dilute acids or alkalies (glutelins). There is a class called prolamines, which are especially abundant in wheat, rye, barley, and maize, which are insoluble in water or salt solutions, but dissolve readily in 70–80 per cent alcohol.

Nearly all proteins contain sulphur, and a few also contain phosphorus; the latter occurs only in milk and in eggs.

244. The amino acids, which are found as constituents of the proteins which form the most prominent constituents of both plants and animals, have been described in their proper relation to other compounds, but may be here grouped together for comparison and contrast.

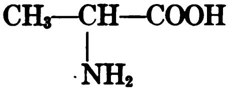
Aliphatic amino acids:

Glycocoll or glycine, aminoacetic acid (**63**).



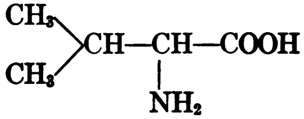
$$\underset{\displaystyle NH_2}{\underset{|}{CH_2}}-COOH$$

Alanine or α-aminopropionic acid (**69**).

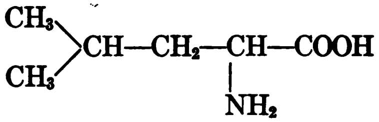


$$CH_3-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

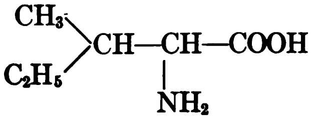
Valine or aminoisovalerianic acid (**73**).



Leucine or α-aminoisobutyl acetic acid (**75**).

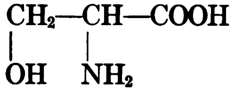


Isoleucine or α-amino-β-ethyl-butyric acid (**76**).



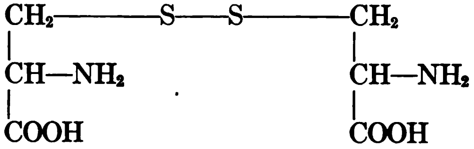
Derivatives of alanine:

Serine or β-hydroxy-α-aminopropionic acid (**69**).



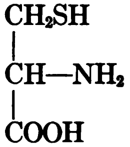
$$\begin{array}{lcl} CH_2 & — & CH—COOH \\ | & & | \\ OH & & NH_2 \end{array}$$

Cystine or di-β-thio-α-aminopropionic acid (**69**).



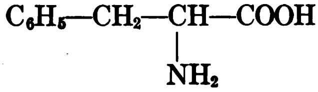
$$\begin{array}{lcccl} CH_2 & — & S—S & — & CH_2 \\ | & & & & | \\ CH—NH_2 & & & & CH—NH_2 \\ | & & & & | \\ COOH & & & & COOH \end{array}$$

On hydrolysis this acid is transformed into two molecules of *cysteine*.



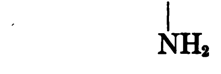
$$\begin{array}{l} CH_2SH \\ | \\ CH—NH_2 \\ | \\ COOH \end{array}$$

Phenylalanine or β-phenyl-α-aminopropionic acid (**206**).



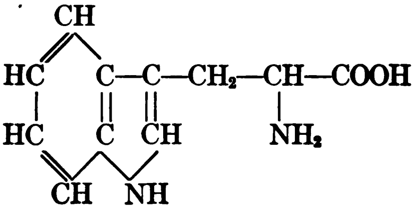
$$\begin{array}{ll} C_6H_5—CH_2— & CH—COOH \\ & | \\ & NH_2 \end{array}$$

Tyrosine, or α-amino, β-oxyphenyl propionic acid or paraoxyphenyl alanine (**185, 199**).

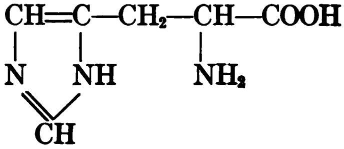


$$\begin{array}{ll} HO—C_6H_4—CH_2— & CH—COOH \\ & | \\ & NH_2 \end{array}$$

Tryptophane, or β-indole-α-aminopropionic acid (**227**).

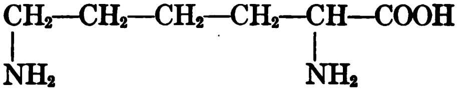


Histidine, or β-imidazolyl-α-aminopropionic acid (**138**).



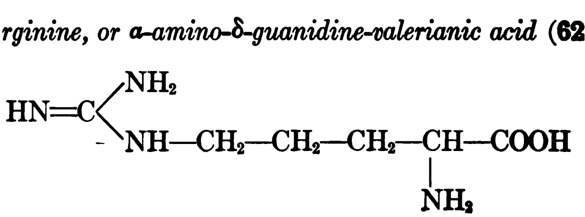
Diamino acids:

Lysine, or α- ε- diamino-caproic acid (**74**).



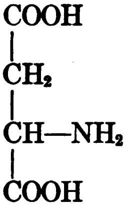
$$\underset{NH_2}{\underset{|}{CH_2}}-CH_2-CH_2-CH_2-\underset{NH_2}{\underset{|}{CH}}-COOH$$

Arginine, or α-amino-δ-guanidine-valerianic acid (**62**).



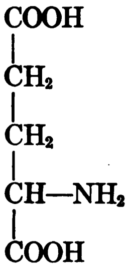
Dibasic acids:

Aspartic acid or aminosuccinic acid (**104**).



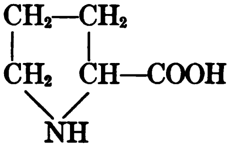
$$\begin{array}{l}\mathrm{COOH}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH{-}NH_2}\\ |\\ \mathrm{COOH}\end{array}$$

Glutamic, glutaminic, or α-aminoglutaric acid (**106**).

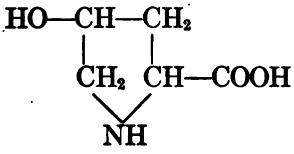


$$\begin{array}{l}\mathrm{COOH}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH_2}\\ |\\ \mathrm{CH{-}NH_2}\\ |\\ \mathrm{COOH}\end{array}$$

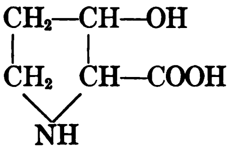
Proline, or α-pyrrolidine-carboxylic acid (**118**).



Oxyproline or β-oxy-α-pyrrolidine-carboxylic acid (**119**).



or



245. Molecular Weights of Proteins. — It has long been known that the proteins are very complex substances with very high molecular weights. Many of the proteins derived from plant and animal tissues certainly have molecular weights of fifteen thousand or higher. There are several ways of arriving at a conclusion as to the size of the molecule. Osborne has studied the problem from the content of sulphur in proteins. This is present in most proteins as cystine, which contains two atoms of sulphur. The atomic weight of sulphur is 32, and two atoms equal 64. If a protein contains 1 per cent of sulphur, its molecular weight would be 6400; if but 0.5 per cent of sulphur, 12,800.

Schulz in 1898 made a study of the effects of heating sulphur compounds of various types with 30 per cent sodium hydroxide and arrived at the following conclusions: Sulphur bound in the linkage $\equiv C-SH$ (mercaptans) is in general not decomposed. Sulphur bound in the form $=C=S$ is decomposed but without the formation of metallic sulphides.

Sulphur bound in the form $\equiv C-S-C\equiv$ is partly decomposed but without the formation of metallic sulphides.

Sulphur bound in the form of $\equiv C-S-S-C\equiv$ is set free by the action of the alkali in the form of H_2S, which in the presence of the alkali forms metallic sulphide. This he designated loosely bound sulphur.

Schulz discovered that when proteins are boiled with sodium hydroxide in an oxygen-free atmosphere (by passing illuminating gas through the apparatus) only a part of the sulphur is set free as hydrogen sulphide, which he determined after acidifying the solution by distilling and weighing as a metallic sulphide. This means that only a part of the sulphur in the protein molecule is present as cystine. Osborne later applied this method to a large number of proteins and with the results shown in the following table:

Protein	Total Sulphur %	Loosely Bound Sulphur		Relation of the Atoms	
		Calculated %	Found %	Firmly Bound	Loosely Bound
Legumin (pea)	0.385	0.193	0.165	1	1
Oxy-Hb. (horse)	0.390	0.195	0.190	1	1
Globin (horse)	0.420	0.210	0.200	1	1
Vignin (pea)	0.426	0.213	0.214	1	1
Amandin (date)	0.429	0.213	0.217	1	1
Oxy-Hb. (man)	0.568	0.379	0.335	1	2
Zein (maize)	0.600	0.200	0.212	2	1
Glycinine (soy bean)	0.710	0.355	0.320	2	2
Hordein (barley)	0.847	0.423	0.348	2	2
Edestin (hemp seed)	0.880	0.440	0.347	2	2
Gliadin (wheat)	1.027	0.629	0.619	2	3
Ovovitellin (egg yolk)	1.028	0.410	0.348	3	2
Excelsin (para nut)	1.086	0.430	0.350	3	2
Serum globulin (horse)	1.110	0.666	0.630	2	3
Fibrin	1.100	0.440	0.380	3	2
Ovalbumen (egg white)	1.616	0.609	0.491	5	3
Serum albumin (man)	1.930	1.498	1.280	2	7

Nothing whatever is known concerning the nature of the sulphur which is combined in the proteins in what is termed in the literature "firmly bound" form. There can be little doubt, however, that there exists a sulphur-containing complex in proteins which has not yet been identified.

From a complete elementary analysis of a long list of proteins Osborne deduced the formulæ and molecular weights as shown in the following table:

Percentage Composition						Formula					Molecular Weight
C	H	N	S	O		C	H	N	S	O	
					Plant Proteins						
51.30	6.90	19.32	0.429	22.05	1. Amandin . . .	638	1030	206	2	206	14930
52.64	6.95	17.25	0.426	22.73	2. Vignin	660	1040	185	2	214	15038
51.72	6.95	18.04	0.385	22.90	3. Legumin . . .	718	1158	214	2	238	16642
55.23	7.26	16.13	0.600	20.78	4. Zein	736	1161	184	3	208	15993
52.12	6.93	17.53	0.710	22.71	5. Glycinin . . .	780	1248	206	4	255	17700
54.29	6.80	17.21	0.847	20.53	6. Hordein	675	1014	181	4	194	14880
51.50	7.02	18.69	0.88	21.91	7. Edestin	624	1021	193	4	199	14523
55.03	6.67	16.26	0.84	21.20	8. Bynin	706	1026	180	4	204	15410
52.72	6.86	17.66	1.027	21.73	9. Gliadin	685	1068	196	5	211	15568
52.18	6.92	18.30	1.086	21.51	10. Excelsin . . .	642	1018	192	5	198	14738
53.02	6.84	16.80	1.280	22.06	11. Leukosin . . .	663	1026	180	6	207	15006
					Animal Proteins						
54.98	7.20	16.89	0.42	20.51	12. Globin	700	1098	184	2	196	15274
52.68	6.83	16.91	1.10	22.48	13. Fibrin	645	1004	178	5	207	14708
52.71	7.01	15.85	1.11	23.32	14. Serumglobulin .	628	1002	160	5	209	14310
52.93	6.90	16.66	1.25	22.26	15. Fibrinogen . . .	679	1062	183	6	207	15276
52.82	7.11	16.67	1.27	22.03	16. Myosin	660	1074	181	6	208	15048
52.75	7.10	15.51	1.616	23.02	17. Ovalbumin . . .	696	1125	175	8	220	15703
52.19	7.18	15.77	1.73	23.13	18. Lactalbumin . .	644	1064	166	8	214	14792
52.99	7.01	15.93	1.93	22.14	19. Serumalbumin .	662	1051	171	9	207	14989
52.25	6.65	15.88	2.25	22.95	20. Serumalbumin .	684	1045	178	11	225	15697
54.64	7.09	17.38	0.39	20.16	21. Oxyhæmoglobin .	758	1181	207	2	210	16655
54.57	7.11	16.38	0.568	21.04	22. Oxyhæmoglobin .	758	1185	195	3	219	16667
53.13	7.06	15.78	0.800	22.37	23. Casein	708	1130	180	4	224	15982
51.56	7.12	16.23	1.028	23.24	24. Ovovitellin . . .	671	1112	182	5	227	15628

1. Almond
2. Pea
3. Bean
4. Maize
5. Soy bean
6. Barley
7. Hemp seed
8. Malt
9. Wheat
10. Paranut
11. Wheat
12. Ox
13. Ox
14. Horse
15. Horse
16. Muscle
17. Egg
18. Cow's milk
19. Horse
20. Man
21. Horse
22. Man
23. Cow's milk
24. Egg yolk

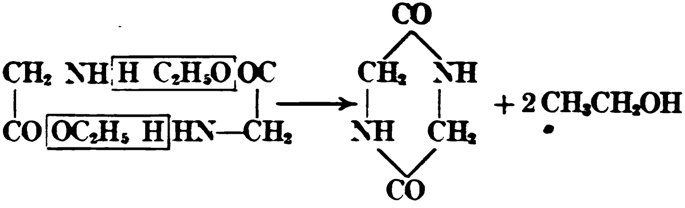
Similar computations of the molecular weight of proteins can be made on the basis of their content of any peculiar group. Thus the hæmoglobin of the blood has the capacity of combining with oxygen of the air in the lungs and of giving up this oxygen in the tissues for the purpose of the oxidations which must go on during metabolism. It can also combine with carbon monoxide. From the combining power of this protein for either of these substances a simple calculation gives the molecular weight, provided the assumption is correct that one molecule of the hæmoglobin combines with one molecule of oxygen or of carbon monoxide.

The molecular weight of carbon monoxide is 28. On the assumption just stated, the ratio $28 : x :: w : 1$, x equals the molecular weight where w is the weight of carbon monoxide which combines with one gram of the protein. By this method the value 16,669 has been secured for carbon monoxide hæmoglobin, and by the oxygen method the value for oxyhæmoglobin was found to be 15,200.

The molecular weights of the amino acids are: glycocoll 75, alanine 89, valine 117, leucine 131, serine 105, cystine 240, phenylalanine 165, tyrosine 191, tryptophane 204, histidine 155, lysine 146, arginine 161, aspartic acid 133, glutamic acid 147, proline 115, and oxyproline 131. The mean of these is 142.7. Since with very few exceptions each of the amino acids named are represented among the digestion products of proteins, it is evident that in general a group of about one hundred amino acids of average molecular weight would give a complex having a molecular weight of about 15,000. This may be accepted as the approximate size of the protein molecule.

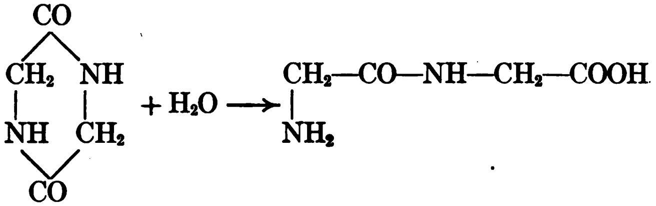
246. Structure of the Proteins. — The manner in which the amino acids are bound together in the molecule was long a mystery, but is now pretty well understood. Light may be thrown on this problem in a number of ways, the most profitable among which has been the cleavage of the giant protein molecule by hydrolysis either with digestive enzymes or by acids or alkalies. This type of decomposition progresses in an orderly fashion, yielding progressively smaller and smaller molecules to which the names proteoses and peptones have been applied, then still simpler complexes called peptides, and finally amino acids.

When the free amino acids have been formed they can be caused to unite again by appropriate methods in the laboratory, and thus a partial synthesis of protein-like compounds can be accomplished. Thus, when the ethyl ester of glycocoll is allowed to stand a few days in water solution, alcohol and glycine anhydride are formed. In this process two molecules of glycocoll are condensed to form a cyclic structure.



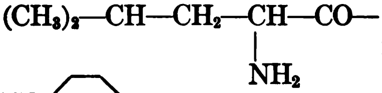
2 molecules of glycocoll ester Glycine anhydride Alcohol

This substance is crystalline and difficultly soluble in cold water. It is readily hydrolyzed when heated for a short time with dilute hydrochloric acid, in which process it takes up one molecule of water, forming the *dipeptide* glycyl-glycine.



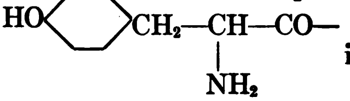
Glycine anhydride **Glycyl-glycine**

Emil Fischer introduced a system of nomenclature for the peptides which describes their structure as well as indicates the amino acids of which they are composed. The amino acid less the —OH of the carboxyl group is given the name of the amino acid with the ending *ine* changed to *yl*. Thus, $NH_2\text{—}CH_2\text{—}CO\text{—}$is glycyl;



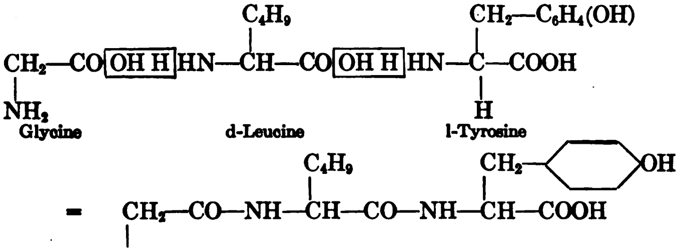
$$(CH_3)_2\text{—}CH\text{—}CH_2\text{—}\underset{NH_2}{\underset{|}{CH}}\text{—}CO\text{—}$$

is leucyl;



is tyrosyl, etc.

The amino acids are combined in the peptides and proteins by the loss of water between the carboxyl group of one and the amino group of another:


C₄H₉
CH₂—C₆H₄(OH)
CH₂—CO OH H HN—CH—CO OH H HN—C—COOH
NH₂
H
Glycine
d-Leucine
l-Tyrosine
C₄H₉
CH₂
OH
= CH₂—CO—NH—CH—CO—NH—CH—COOH
NH₂

Glycyl-d-leucyl-l-tyrosine (tripeptide)

TRYPSIN CLEAVES THE FOLLOWING:	TRYPSIN DOES NOT CLEAVE THE FOLLOWING:
l-leucyl-l-leucin	leucyl-glycin
l-leucyl-d-glutamic acid	l-leucyl-glycin
glycyl-l-tyrosin	leucyl-l-leucin
*leucyl-l-tyrosin	l-leucyl-d-leucin
*alanyl-glycyl-glycin	d-leucyl-l-leucin
*leucyl-glycyl-glycin	amino-iso-valeryl-glycin
*glycyl-leucyl-alanin	glycyl-phenyl-alanin
*alanyl-leucyl-glycin	phenyl-alanyl-glycin
dialanyl-cystin	alanyl-phenyl-alanin
dileucyl-cystin	phenyl-alanyl-alanin
tetraglycyl-glycin	leucyl-phenyl-alanin
glycyl-d-alanyl-glycyl-tyrosin	diglycyl-glycin
	triglycyl-glycin
	dileucyl-glycyl-glycin

Those peptides which are marked with a star are derived from the racemic form of the amino acid, *e.g.* of equal molecules of the d- and l- forms. In such cases the cleavage by the enzyme is not complete, but affects only those complexes which contain the optical form of the amino acid which occurs in nature.

Other factors which determine whether the peptide can be attacked by the enzyme are the kind of amino acid and the position in the chain. The alanyl group favors the cleavage, as do also the tyrosine and isoserine groups when these are at the end of the chain.

The specific relation between the structure of the peptide and that of the enzyme is apparent when alanyl-glycine is digested by trypsin but glycyl-alanine is not.

* Signifies the racemic compound.

Furthermore, the length of the chain may determine whether enzymatic cleavage can be effected. Thus, triglycyl-glycine is not attacked by trypsin, whereas tetraglycyl-glycine is.

247. The Complexity of the Protein Molecule. — The property of the simpler peptides of being hydrolyzed by organic catalysts of the class of the enzymes *when composed of the optical forms of the amino acids found in nature, but not otherwise,* and of yielding amino acids on hydrolysis with acids, affords convincing evidence that the natural proteins are structurally similar to the synthetic peptides, but of higher molecular weight. The view that the protein molecule is very complex is supported by a number of facts:

1. The large number of amino acids (14–17) which proteins yield on hydrolysis. The union of even one molecule of each of these to form a hexadecapeptide would form a complex having a molecular weight of over two thousand, since the mean molecular weight of all the amino acids found in nature is about 140.

2. The colloidal nature of the proteins when in solution. This manifests itself in the failure of protein solutions, even when very concentrated, to show a lowering of the freezing point as compared with pure water. Since the lowering of the freezing point depends on the number of dissolved particles in a given amount of the solvent, the failure of concentrated solutions to be affected as to freezing point, indicates that the particles in solution are few and very large.

3. The molecules of protein are sufficiently large to

cause them to scatter the light which passes into their solutions, and cause the molecules to appear as luminous points. These are rendered visible to the eye in the ultra microscope. In this instrument the field is illuminated at right angles to the line of vision. The principle is well illustrated by the position in which one must stand in order to see motes in the air of a darkened room into which a beam of light enters through a small aperture. Dust which is invisible to the naked eye in a room well illuminated is easily seen floating in a sunbeam when the latter is viewed at right angles to its path. The ultra microscope makes use of this principle and thus renders molecules of colloidal substances in solution visible as points of illumination.

Solutions of salts, acids, bases, sugars, etc., when viewed free from dust particles appear perfectly homogeneous in the ultra microscope. The beam of light passes through them without any interference by the particles. Substances of about the molecular weight of raffinose, $C_{18}H_{32}O_{16}$ (molecular weight 440), show some tendency to scatter light and to become visible in the ultra microscope.

E. Fischer has synthesized by the methods described a complex peptide containing eighteen amino-acid radicals and having a molecular weight of 1213. This octadeca peptide was l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octoglycyl-glycine. It was soluble in 100 parts of boiling water, and non-crystalline. Its solution foamed like that of a protein, and it was precipitated by the addition of ammonium sulphate, a property common to all soluble proteins and to certain of their digestion products, the proteoses.

The number of proteins which are theoretically possible of formation by the peptide union of sixteen amino acids is very great. With four different amino acids 24 peptides are possible. If the letters a, b, c, and d represent each a different amino acid, they may be arranged in peptide union as follows:

a—b—c—d
a—b—d—c
a—c—b—d
a—c—d—b
a—d—b—c
a—d—c—b
b—a—c—d
b—a—d—c
b—c—a—d
b—c—d—a
b—d—a—c
b—d—c—a
c—a—b—d
c—a—d—b
c—b—a—d
c—b—d—a
c—d—a—b
c—d—b—a
d—a—b—c
d—a—c—b
d—b—a—c
d—b—c—a
d—c—a—b
d—c—b—a

While half of these combinations may at first sight appear to be duplicates of the remaining half because they are the same when read backward, it should be borne in mind that, in such cases, the terminal groups in a peptide are dissimilar although derived from the same amino acid. One has its amino group free and its carboxyl in union, while with the other the reverse is true.

When two amino acids of a kind and two unlike ones make up the four, the possibilities for isomers are twelve. It has been calculated that for sixteen amino acids the number of isomers theoretically possible is 20,922,789,888,000. This accounts for the great variety of proteins found in nature.

248. The Solubility Relations of the Proteins. — If a finely ground seed, wheat for example, be extracted with distilled water there will be extracted a certain amount of protein bodies of three classes. This can be demonstrated in several ways. If some of the filtered water extract be rendered slightly acid and heated, it will be found that when the temperature reaches 50–60° C. the solution becomes turbid and there separates a voluminous precipitate consisting principally of the albumin leucosin. This protein constitutes but 0.4 per cent of the weight of the seed. In a water extraction there is always removed from the seed a certain amount of inorganic salts, and as will be seen, there is a class of proteins which dissolve in water containing even small amounts of inorganic salts, although they are insoluble in pure water.

If a second portion of the filtered extract of the seed be placed in a bag of parchment paper or in the bladder of an animal, and surrounded by distilled water, the application of suitable qualitative tests will soon reveal the fact that certain inorganic ions as Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-, $HPO_4^=$, $SO_4^=$, are passing through the semipermeable membrane, from the solution inside to the distilled water without. If the latter is frequently changed, the salts which were extracted from the seed will all be removed from the protein-containing extract. Suitable tests, as the coagulation test, Millon's reaction, Hopkins-Cole's reaction, demonstrate, by the production of a color, the presence of tyrosine and tryptophane respectively. Both of these amino acids are nearly constantly found in proteins. The biuret reaction shows the presence of certain characteristic organic linkages. These tests reveal the fact that while the inorganic salts have passed out of the bag the protein has not. After complete dialysis, however, it will be found that a small amount of protein material has separated from the seed extract and remains deposited in the bag as an insoluble precipitate. This is soluble in water containing inorganic salts, but not in distilled water. It is called *globulin*. In wheat the globulin fraction amounts to about 0.6 per cent of the seed, but there is not enough salt extracted from the seed to bring it all into solution. A thorough extraction must be made with dilute sodium chloride solution, in order to free the seed from globulin.

The residue of the wheat after complete extraction with distilled water and with salt solution will still yield a large amount of protein when extracted with alcohol of 70 per cent strength. The protein thus extracted can be separated out by sufficient dilution of the alcohol by the addition of water, or by pouring the dilute alcoholic solution of the protein into absolute alcohol.

Beans and peas contain no alcohol-soluble proteins. After removal of both the albumin and the globulin fractions the bean will still yield a large portion of its original protein content to a very dilute solution of sodium hydroxide (0.2 per cent). On neutralizing the solution with acid the alkali-soluble proteins, which are known as *glutelins*, separate out. In this manner nearly all of the proteins can be removed from the seed, leaving behind the cellulose, hemicelluloses, starch, etc.

The proteins which are extracted by water are not completely coagulated by heat, even when the conditions of acidity are most favorably adjusted. There are found in all seeds a certain amount of protein-like substances which can be " salted out " by adding ammonium sulphate to saturation, but are not coagulable by heat. These substances are collectively known as *proteoses*.

Although there are now available quantitative methods for the determination of a few of the amino acids yielded by proteins, this is possible only for arginine, histidine, lysine, glutamic acid, and cystine. Fairly good determinations can be made of several others, especially of glycocoll, leucine, tyrosine, and proline, while the remainder cannot be estimated in a quantitative way.

249. Classification of the Proteins. — While it is known that the yield of particular amino acids by certain proteins varies widely, it is not yet possible to propose a satisfactory classification of the proteins of the animal and plant kingdom on a chemical basis. The best that can be done is to classify the proteins and their derivatives according to their solubilities in various solvents. The following classification has been adopted by American bio-chemists and physiologists:

Simple Proteins

By "protein" is meant a substance which yields only α-amino acids on hydrolysis. The term applies only to the complexes of high molecular weight and not to the simpler peptides.

(*a*) *Albumins:* Proteins soluble in pure water and coagulable by heat. They coagulate nearly completely from slightly acid solutions, incompletely from neutral, and not at all from distinctly alkaline solutions. Familiar examples are egg albumen, serumalbumin of blood, and lactalbumin of milk. There are many vegetable albumins.

(*b*) *Globulins:* Proteins not soluble in pure water, but soluble in solutions of the salts of strong acids with strong bases. Such proteins are common in seeds, and in the blood of animals. The globulin of blood serum is specific in its character for each species of animal.

(*c*) *Glutelins:* Proteins insoluble in all neutral solvents, but soluble in very dilute acids and alkalies. These are especially prevalent in certain seeds, as peas, beans, etc., but are found in all seeds.

(*d*) *Protamines:* Proteins soluble in alcohol of 70–90 per cent strength, but insoluble in water, or nearly so, and in absolute alcohol and other neutral solvents, such as solutions of inorganic salts. This type of proteins is found only in seeds. Examples are *zein* from the maize kernel, *gliadin* of wheat, *hordein* of barley, etc.

(*e*) *Albuminoids:* Proteins which are chemically similar in their constitution to those already described, but characterized by their insolubility in all neutral solvents. They constitute the protein portion of ligaments, connective tissue (collagen), tendon, horn, nails, hair, wool, etc. They are not hydrolyzed by the digestive enzymes which accelerate the hydrolysis of other classes of proteins. English chemists designate these as *scleroproteins.*

(*f*) *Histones:* Proteins soluble in water but insoluble in very dilute ammonia, and, in the absence of ammonium salts, insoluble in stronger ammonia solutions. They yield precipitates with solutions of other proteins, and are coagulable by heat, the coagulum being easily soluble in dilute acids. While they yield all or nearly all the amino acids found in proteins generally, the yield of arginine, lysine, and histidine is particularly high, which gives them their basic character. In this respect they stand midway between the proteins (*a*) to (*e*) inclusive on the one hand and the protamines (*g*) on the other. Histones are found in the blood corpuscles, the protein *globin* in hæmoglobin being a histone. Other examples are the histone from the thymus gland and from the partially ripe testicles of fishes, etc.

(*g*) *Protamines:* These are complex polypeptides of smaller molecular weight than the proteins of the preceding groups. They are soluble in water and do not coagulate on being heated. They possess strongly basic properties and form stable salts with strong mineral acids. They likewise form insoluble compounds with aqueous solutions of other proteins. On hydrolysis they yield but few amino acids, among which the basic acids, arginine, histidine, and lysine predominate. They are the simplest of the natural proteins and have been found only in the heads of the spermatozoa of fishes. The sperm of mammals contains histones, but no protamines.

Conjugated Proteins

Substances which contain the protein molecule united to some other molecule or molecules otherwise than as a salt.

(a) Nucleoproteins. Compounds of one or more molecules of protein with nucleic acid.

(b) Glycoproteins. Compounds of the protein molecule with a substance or substances containing a carbohydrate group other than a nucleic acid, e.g. mucins and mucoids.

(c) Phosphoproteins. Compounds of the protein molecule with some, as yet unidentified, phosphorus-containing substance other than a nucleic acid or lecithin. They yield on hydrolysis the usual amino acids derived from proteins, and in addition orthophosphoric acid. Phosphoproteins have been found only in the milk of animals and in egg yolk. The casein of milk and vitellin of egg yolk are examples of phosphoproteins.

(d) Hemoglobins. Compounds of the protein molecule with hematin or some similar substance. The hemoglobin of the red blood corpuscles is an example.

(e) Lecithoproteins. Compounds of the protein molecule with lecithins. Definite knowledge concerning these is extremely meager.

Derived Proteins

1. Primary Protein Derivatives

Derivatives of the protein molecule apparently formed through hydrolytic changes which involve only slight alteration of the protein molecule.

(a) Proteans. Insoluble products which apparently result from the incipient action of water, very dilute acids, or enzymes. *Edestan* from *edestin* is an example.

(*b*) *Metaproteins:* Products of the further action of acids or alkalies whereby the molecule is so far altered as to form products soluble in very weak acids and alkalies, but insoluble in neutral fluids. *Acid metaprotein* (*acid albuminate*), *alkali metaprotein* (*alkali albuminate*).

(*c*) *Coagulated Proteins:* Insoluble products which result from (1) the action of heat on their solutions, or (2) by the action of strong alcohol on the protein.

2. *Secondary Protein Derivatives.*

Products of the further hydrolytic cleavage of the protein molecule.

(*a*) *Proteoses:* Soluble in water, non-coagulable by heat, and precipitated by saturating their solutions with ammonium or zinc sulphate.

(*b*) *Peptones:* Soluble in water, non-coagulable by heat, but not precipitated by saturating their solutions with ammonium sulphate.

(*c*) *Peptides:* Definitely characterized combinations of two or more amino acids, the carboxyl group of one being united with the amino group of the other, with the elimination of a molecule of water, *dipeptides, tripeptides, tetrapeptides*, etc.

250. The Chemical Analysis of Proteins. — The biological value of a protein depends on the proportions of the several amino acids which it yields on hydrolysis. The process of protein digestion is one of hydrolysis of the giant protein molecule into simpler and simpler fragments, the amino acids being the final products. The importance of the proteins in the nutrition of animals and man makes it highly desirable that methods of analysis be devised by means of which the content of each of the amino acids can be quantitatively determined. Up to the present time efforts in this direction have been but partially successful. During the last quarter of the nineteenth century progress in the study of the proteins was slow, but a considerable number of the amino acids became known and the general structure of the proteins, *i.e.* that they consisted of amino acids in peptide union, was made clear. The first method developed which was capable of differentiating the proteins on the basis of their composition was that described by Hausmann in 1899. It determined (1) the three basic amino acids, arginine, histidine, and lysine, together as a group, by showing what part of the total nitrogen of the protein molecule existed in these complexes; (2) the fraction of the total nitrogen in the protein which existed as mono-amino acids; (3) the nitrogen in the form of the acid amide group $CONH_2$; (4) the humin nitrogen, or that which exists in the black, insoluble material which is always formed when proteins are boiled with acids. The procedure is briefly as follows:

Hausmann Method.—1. Hydrolysis of the protein (1 gram) with 20 per cent hydrochloric acid until it is completely converted into amino acids. It is then evaporated nearly to dryness to remove the greater portion of the hydrochloric acid.

2. The residue is transferred to a flask with water and cream of magnesia (MgO with water) added in amount to neutralize the remaining acid and to make the solution slightly alkaline. It is then distilled, and the ammonia which passes over is collected in standard acid and estimated. The ammonia formed represents the nitrogen which existed in the protein as acid amide groups.

3. After the completion of the ammonia estimation the excess of MgO together with the black insoluble "humin" substances formed in operation 1 are filtered off and thoroughly washed with water. The nitrogen content of the "humin" material is then estimated

by the Kjeldahl method. It has been shown that this represents nearly the nitrogen derived from tryptophane.

4. The filtrate from the "humin" is concentrated to 100 c c., cooled to 20°, 5 grams of sulphuric acid added and then 30 c.c. of a solution containing 20 grams of phosphotungstic acid and 5 grams of sulphuric acid per 100 c.c. After 24 hours the precipitate is filtered off and washed with a dilute phosphotungstic acid (sulphuric acid solution according to a prescribed degree of thoroughness). This procedure precipitates the "diamino acids" nearly completely. The nitrogen in this precipitate is reported as "basic" or diamino-acid nitrogen.

5. The filtrate from the diamino acids is examined by the Kjeldahl method for its nitrogen content and the nitrogen so found was termed "non-basic" nitrogen and was interpreted as consisting principally of the monoamino acids.

Later studies by Van Slyke have shown that in the main the interpretation put upon the data obtained by the Hausmann method is correct. He showed that unaltered cystine is precipitated along with the three basic amino acids. A considerable part of this acid is decomposed by boiling acid during the hydrolysis.

The data obtained by Osborne and Harris by their modified Hausmann method show in such a marked fashion the differences in the distribution of the nitrogen of the protein molecule, between basic or diamino acids and mono-amino acids, and in the yield of "humin" and ammonia nitrogen that their table is reproduced here, the data being recalculated, so as to express the nitrogen in the special forms in per cent of the total nitrogen.

251. The Origin of the Humin Nitrogen Formed during Hydrolysis. — Gortner and Blish made the observation that zein, the principal protein of the maize kernel,

DISTRIBUTION OF NITROGEN IN PROTEINS
TOTAL N=100

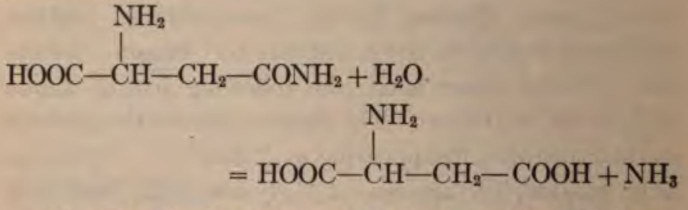
	NH_3 N	BASES N	MONO-AMINO ACIDS N	HUMIN N	TOTAL N
Conalbumen (egg white)	7.51	25.82	65.11	1.61	16.11
Phaseolin (bean) . . .	10.74	24.50	62.85	1.79	16.20
Glycinine (pea) . . .	12.09	22.63	64.58	.68	17.45
Legumelin (pea, bean) .	6.46	23.06	68.12	2.36	16.09
Leucosin (wheat) . . .	6.85	20.67	69.87	2.54	16.93
Glutenine (wheat) . .	18.86	11.72	68.32	1.09	17.49
Gliadin (rye)	23.78	5.49	70.27	.79	17.66
Hordein (barley) . . .	23.30	4.47	69.96	1.33	17.21
Zein (maize)	18.41	3.03	77.56	.99	16.13
Globulin (wheat) . . .	7.72	37.14	53.39	1.52	18.39
Globulin (coca nut) . .	7.35	32.79	59.09	.75	18.48
Globulin (squash seed) .	6.91	32.25	59.64	1.18	18.51
Globulin (cotton seed) .	10.30	30.63	59.06	—	18.64
Edestin (hemp seed) . .	10.08	31.70	57.83	.64	18.64
Excelsin (para nut) . .	8.87	31.47	59.94	.92	19.30
Corylin (hazel nut) . .	11.57	30.26	56.31	.89	19.00
Amandin (almond) . .	16.04	21.84	60.08	.89	19.00
Globulin (castor bean) .	10.45	30.08	58.66	.64	18.75
Corylin (walnut) . . .	9.44	28.71	61.09	.79	18.84
Congluten (*a*) (lupine) .	11.84	29.05	58.00	1.00	17.90
Congluten (*b*) (lupine) .	14.55	28.17	56.56	.76	18.21
Legumin (pea)	9.40	28.82	60.27	.94	17.97
Globulin (flaxseed) . .	10.82	25.81	62.06	1.18	18.48
Vicilin (pea, bean) . .	10.40	27.76	60.60	1.22	17.11
Vignin (pea)	11.07	25.39	62.66	1.45	17.25
Globulin (sunflower seed)	13.83	22.98	62.00	1.29	18.58
Vitellin (egg yolk) . .	7.67	28.56	62.41	1.35	16.28
Casein (cow's milk) . .	10.30	22.84	66.00	1.34	15.62
Ovalbumen (egg) . . .	8.64	21.27	68.21	1.87	15.51
Chicken muscle . . .	7.45	29.98	59.85	2.43	16.09
Halibut muscle . . .	6.70	30.18	60.73	2.37	16.40
Scallop muscle	6.33	26.51	64.81	2.34	17.05
Beef muscle	5.50	27.32	64.52	2.65	16.18

when heated with hydrochloric acid in the presence of rbohydrates according to the usual procedure in the hydrolysis of proteins yielded, about 0.50 per cent of the total nitrogen of the protein appeared in the humin fraction. When zein, *tryptophane,* and carbohydrate were heated with acid 16.5 per cent of the total nitrogen was in the "humin." Zein, histidine, and carbohydrate gave about the same "humin" nitrogen value as did zein alone. Now, zein contains no tryptophane, and Gortner and Blish were led to conclude that the amino acid tryptophane was the source of the "humin" nitrogen. The correctness of this view was confirmed by the observation that tryptophane when heated with carbohydrate and acid yielded 86.56 per cent of its nitrogen as black insoluble "humin." They proposed this reaction as an approximately quantitative method for the estimation of tryptophane. It is, indeed, the best approach to such a method which we possess.

Further studies by Gortner and Blish and by Roxas have shown that when heated with hydrochloric acid and carbohydrate, alanine, leucine, phenylalanine, proline, and glutamic acid do not contribute to "humin" formation. On the other hand, the following list of amino acids do so contribute. The figures indicate the per cent of their nitrogen disappearing as "humin": Tyrosine, 15.0; cystine, 3.1; arginine, 2.33; lysine, 2.62; histidine, 1.84; tryptophane, 71.0.

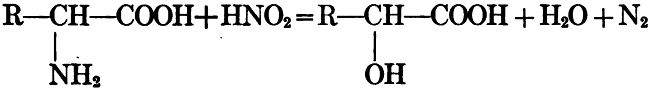
The nature of the reaction by which "humin" is formed is not very clear. *In the absence of carbohydrate tryptophane* does not form humin. The nature of the humin in proteins which contain no carbohydrate group is still unknown.

252. Source of the Ammonia Formed in Protein Hydrolysis. — During the hydrolysis of proteins by digestion with enzymes, no ammonia is formed, but in acid hydrolysis the amount of the total nitrogen of the protein appearing in this form varies in different proteins, from 6 to 23.78 per cent. It has long been known that asparagine and glutamine occur in the juice of seedlings, and their origin has been assumed to be the digestion of the proteins of the resting seed. Osborne, Leavenworth, and Brautlecht have pointed out that the amount of ammonia formed in acid hydrolysis closely agrees in most instances with the theoretical, if it is assumed that one of the two carboxyl groups in glutamic and aspartic acids exists in the protein molecule as an acid amide group. Asparagine and glutamine have not as yet been isolated from proteins, and indeed cannot be through acid hydrolysis, since the amide group is hydrolyzed to carboxyl and ammonia.



$$\mathrm{HOOC{-}\overset{\overset{NH_2}{|}}{C}H{-}CH_2{-}CONH_2 + H_2O = HOOC{-}\overset{\overset{NH_2}{|}}{C}H{-}CH_2{-}COOH + NH_3}$$

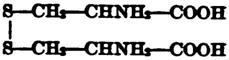
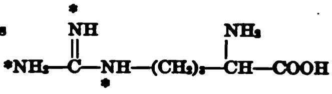
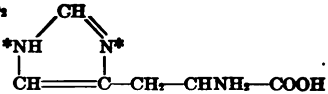
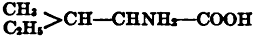
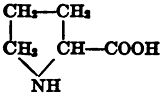
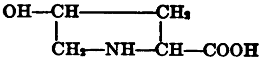
253. The Amino-nitrogen Method of Van Slyke. — D. D. Van Slyke introduced a simple, accurate, and fairly rapid method for the separate estimation of arginine, histidine, lysine, ammonia, and humin nitrogen. In the filtrate from the bases, which are precipitated by phosphotungstic acid, the nitrogen which is present as amino groups is estimated and by difference the non-amino nitrogen, from which the content of proline can be calculated as shown on page 444. The method depends upon the fact that the α-amino group of an amino acid reacts with nitrous acid under appropriate conditions, replacing the NH_2 by hydroxyl:



$$R\text{—}\underset{\substack{|\\ NH_2}}{CH}\text{—}COOH + HNO_2 = R\text{—}\underset{\substack{|\\ OH}}{CH}\text{—}COOH + H_2O + N_2$$

This reaction between a primary amine and nitrous acid has long been known and used for the conversion of primary amines into alcohols (46). Van Slyke's method was based on the older method of Hausmann (250) and represents a very great advance over the latter. Advantage is taken of the fact that nitrous acid does not react with the nitrogen of secondary or tertiary amines, which groupings are found in histidine, proline, and arginine. It also is unable to attack the guanidine complex in arginine. The reaction is carried out in an apparatus which is described in all text-books on physiological chemistry. Nitrous oxide is generated in the apparatus until all the air is expelled before the sample is introduced. The elemental nitrogen which is formed is accurately measured as a basis for calculation.

The nitrogen is freed from oxides of nitrogen and traces of carbon dioxide by washing with alkaline permanganate solution and is then measured and from the volume of gas collected the amino nitrogen is estimated. The following table illustrates the scheme of the analysis:

Precipitated by phosphotungstic acid	**With HNO_2 yield 100 per cent of their N as elemental N**	***Cystine*** ** **(calc. from S content)**	 $\begin{array}{l}S-CH_2-CHNH_2-COOH\\ \vert\\ S-CH_2-CHNH_2-COOH\end{array}$
		Lysine ** **(calc. by difference)**	$NH_2-(CH_2)_4-CHNH_2-COOH$
	Contain non-amino nitrogen	***Arginine*** **With HNO_2 yields ¼ of its N in elemental form**	 $\overset{\overset{*}{NH}}{\Vert}$ ... $^*NH_2-\overset{\overset{*}{NH}}{\overset{\Vert}{C}}-\underset{*}{NH}-(CH_2)_3-\overset{NH_2}{\overset{\vert}{C}H}-COOH$
		Histidine **With HNO_2 yields ⅓ of its N in elemental form**	
Not precipitated by phosphotungstic acid	**With HNO_2 yield 100 per cent of their N as elemental N**	**Glutamic acid,**	$HOOC-CH_2CH_2CHNH_2-COOH$
		Aspartic acid,	$HOOC-CH_2-CHNH_2-COOH$
		Tyrosine,	$HO-C_6H_4-CH_2-CHNH_2-COOH$
		Phenylalanine,	$C_6H_5-CH_2-CHNH_2-COOH$
		Serine,	$HO-CH_2-CHNH_2-COOH$
		Leucine,	$(CH_3)_2=CH-CH_2-CHNH_2-COOH$
		Isoleucine,	 $\begin{array}{l}CH_3\\ C_2H_5\end{array}\!\!>CH-CHNH_2-COOH$
		Valine,	$(CH_3)_2=CH-CHNH_2-COOH$
		Alanine,	CH_3-CHNH_2-COOH
		Glycocoll,	CH_2NH_2-COOH
	With HNO_2 yield no elemental nitrogen	**Proline,**	
		Oxyproline	
		Tryptophane	$C_8H_6N-CH_2-CHNH_2-COOH$

The three atoms in the guanidine group do not react with nitrous acid. However, arginine on heating with strong alkalies yields half the nitrogen of the guanidine complex, first as urea, then as ammonia. This is the basis for the estimation of arginine by Van Slyke's method. (See page 119, arginine decomposition.)

* The nitrogen atoms marked with a star do not react with nitrous acid.

** Cystine is calculated from the sulphur contained in the phosphotungstic precipitate. Arginine is estimated from the ammonia yielded by heating the bases with strong NaOH.

Histidine N = 3/2(total non-amino N of bases − 3/4 Arg. N). Lysine N = total N of bases − (Arg. N + Cyst. N + Hist. N).

RESULTS OF ANALYSIS OF PROTEINS BY THE AMINO-NITROGEN METHOD OF VAN SLYKE

Results expressed in percentages of total nitrogen

	GLIADIN	LACT-ALBUMIN	EDESTIN	GELATIN	FIBRIN	HEMOGLOBIN, OX	HAIR (dog)	RICE PROTEIN	WHEAT PROTEIN	MAIZE PROTEIN
Ammonia N .	24.61	8.60	9.99	2.25	8.32	5.24	10.05	2.22	4.62	3.13
Humin N . .	.58	2.69	1.98	.07	3.17	3.60	7.22			
Cystine N . .	.80	.30	1.49	0.00	.99	?	5.60			
Arginine N . .	5.45	6.20	27.05	14.74	13.86	7.70	15.33	9.15	3.86	3.39
Histidine N .	3.39	2.94	5.75	4.48	4.83	12.70	3.48	3.32	2.02	1.55
Lysine N . .	1.33	12.17	3.86	6.32	11.51	10.90	5.37	4.26	1.58	.97
Amino N in filtrate from bases . . .	51.95	62.30	47.55	55.80	54.20	57.00	47.50			
Non-amino N in filtrate from bases (Proline and Oxyproline) . . .	10.70	3.30	1.70	14.90	2.70	2.90	3.10			
Total N accounted for	98.81	98.50	99.37	98.56	99.58	100.04	97.65			

254. The Method of Kossel for the Estimation of the Basic Amino Acids in Proteins. — The details of the method will not be given here. In principle it depends upon the precipitability of arginine, histidine, and lysine by phosphotungstic acid in acidified solutions of appropriate dilution. The three bases freed from phosphotungstic acid by barium hydroxide are separated by:

(*a*) Precipitating both arginine and histidine as the silver compounds, lysine remaining in the filtrate.

(*b*) Histidine is separated from arginine by the insolubility of its mercury compound. Arginine is ultimately weighed as crystalline arginine nitrate; histidine as the hydrochloride.

(*c*) Lysine is precipitated again with phosphotungstic acid and is afterwards converted into the picrate and weighed as such.

frequency of those amino acids which contain a five-carbon compact structure namely of arginine, histidine, proline and valine, while those cleavage products of proteins containing six carbon atoms, lysine, leucine, and isoleucine, are found only occasionally.

388. Free Amino Nitrogen of the Unhydrolyzed Proteins.—In studying the rate of the liberation of the amino nitrogen from the isolated amino acids while perfecting his method of analysis, Van Slyke observed that the ε-amino group of lysine was acted upon at a slower rate than the α-amino group. Later he and Birchard determined the amount of nitrogen which is set free by the action of nitrous acid upon unhydrolyzed proteins. It was observed that the liberation of elemental nitrogen was in all cases slower than would be expected if α-amino groups were being acted upon. This led to the conclusion that in the unhydrolyzed protein the free amino groups are the ε-amino groups of the lysine contained in the protein, and are the only free amino groups contained therein, all the α-amino groups of the constituent amino acids being bound in peptide linkings.

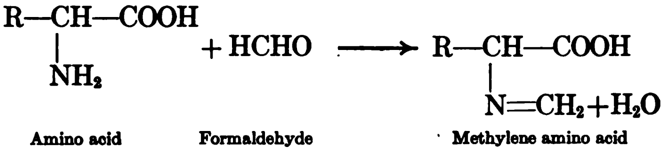
Hartley compared the nitrogen set free by the action of nitrous acid upon the intact albumin and globulins of the serum of the horse and ox with the amount of nitrogen yielded as lysine by these proteins and found the free amino N to equal one half of lysine nitrogen.

Osborne, Van Slyke, Leavenworth, and Vinograd have further investigated this relationship. The data available are shown in the following table:

FREE AMINO NITROGEN OF PROTEINS COMPARED WITH THE LYSINE NITROGEN

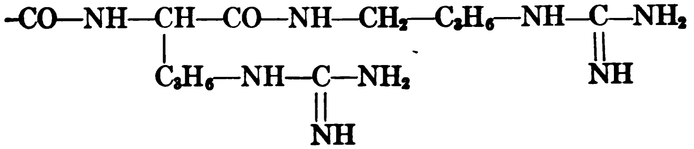
PROTEIN	PER CENT OF TOTAL NITROGEN AS AMINO N	PER CENT OF TOTAL N = ½ THE LYSINE N AS DETERMINED BY VAN SLYKE METHOD
Lactalbumin	6.49	6.10
Rice protein	2.17	2.00
Wheat gliadin	.62	.66

257. The Formol Titration of Sörensen. — The solutions of all of the amino acids except arginine and lysine are nearly neutral. The latter are basic. It is not possible to titrate the amino acids therefore, because of the presence of both amino and carboxyl groups. Sörensen devised a method of doing away with the basic character of the amino group by condensing with it formaldehyde, which converts primary amines into methylene derivatives containing tertiary nitrogen and devoid of basic properties. The following reaction is typical:



$$\underset{\displaystyle NH_2}{\text{R—}\overset{}{\text{CH}}\text{—COOH}} + HCHO \longrightarrow \underset{\displaystyle N{=}CH_2 + H_2O}{\text{R—CH—COOH}}$$

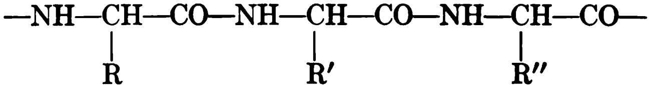
The methylene derivatives now behave like fatty acids with respect to indicators and can be estimated by titration with standard alkali solution. It serves also as a method of estimating the degree to which a protein has evolve any gas, showing that it contains no amino groups other than those of the guanidine complexes in the arginine molecules, Kossel and Cameron propose the following linkage for arginine in the protamine molecule:



$$-CO-NH-\underset{\substack{|\\ C_3H_6-NH-\underset{\substack{\|\\ NH}}{C}-NH_2}}{CH}-CO-NH-CH_2-C_3H_6-NH-\underset{\substack{\|\\ NH}}{C}-NH_2$$

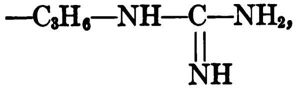
Even in those protamines which contain much lysine, the acid-combining power is too great to be accounted for by the lysine, so that part of it is due to the guanidine complex.

Kossel and Weiss, in consideration of the properties of protamines described above, consider the most probable structural relationship in sturine to be expressed by the following scheme:

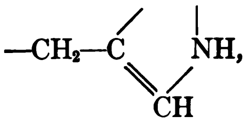


$$-NH-\underset{\substack{|\\ R}}{CH}-CO-NH-\underset{\substack{|\\ R'}}{CH}-CO-NH-\underset{\substack{|\\ R''}}{CH}-CO-$$

in which R, R′, R″ may be

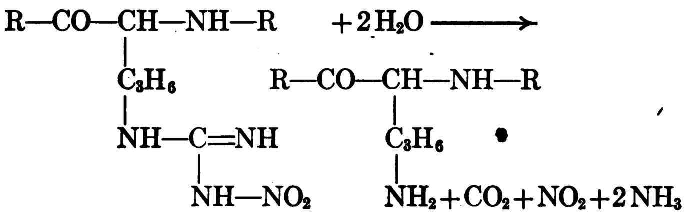


$$-C_3H_6-NH-\underset{\substack{\|\\ NH}}{C}-NH_2,$$



$-CH_3$, or $-C_4H_9$,

complexes which on hydrolysis yield arginine, histidine, lysine, alanine, and leucine, respectively. Concerning the order of combination of the several amino acids, however, nothing can be said. When nitroclupein is allowed to stand at 40° with *n*-sodium hydroxide, nitrous oxide, ammonia, and carbon dioxide are liberated and from the resulting product, on hydrolysis, ornithine is obtained instead of arginine. The decomposition probably follows the following line:



$$R-CO-\underset{\substack{|\\ C_3H_6\\ |\\ NH-\underset{\substack{|\\ NH-NO_2}}{C}=NH}}{CH}-NH-R \quad + 2H_2O \longrightarrow R-CO-\underset{\substack{|\\ C_3H_6\\ |\\ NH_2}}{CH}-NH-R + CO_2 + NO_2 + 2NH_3$$

259. The Glutamic Acid Content of the Proteins. — A striking illustration of the great variation in the amount of a particular amino acid yielded by various proteins is indicated in the table on page 455. The hydrochloric acid salt of glutamic acid is very sparingly soluble in cold concentrated hydrochloric acid and separates out readily in a crystalline form. This amino acid can be estimated quantitatively with greater satisfaction than most of the other monoamino acids, so the data are exceptionally reliable.

There is much reason to believe that glutamic acid does not occur as such in the protein molecule, but in the form of its half amide, glutamine (**107**).

COMPOSITION OF THE PROTAMINES

In per cent of the total nitrogen

PROTAMINE SOURCE	AMMONIA N	ARGININE N	HISTIDINE N	LYSINE N	MONO-AMINO ACID N	TYROSINE N	TRYPTOPHANE N	LEUCINE N	PROLINE N	VALINE N	SERINE N	ALANINE N
Percin (yellow perch)	0	78.1	5.6	0	9.8	0	0		+	+	—	
Percin (pike perch)	0	76.3	6.7	0	10.7	0	0		+	+	—	
Thynnin (tuna) . .	0	79.5	0.0	0	11.0	0.6			+	+	—	
Scombrin (mackerel)	0	88.8	0.0	—		+	—	—	—	—	—	
Xyphin (swordfish)	0	81.5	0.0	0	14.0	+	—	—	—	—	—	
Salmin (Chinook salmon)		87.8		—	9.4	—	—	—	10.83	5.35	8.7	
Coregonin (white-fish)	0	87.3	0.0	0	9.4	—	—	—	—	—	—	
Salvelin (lake trout)	0	88.9	0.0	0	7.1	—	—	—	—	—	—	—
Esocin (pike) . .	0	86.3	0.0	0	11.3	0	0					—
Sturin (sturgeon) .	0	63.5	11.8	8.4		0	0	+	—	—	—	+
Clupein (herring) .	0	88.0	0.0	0		0	0	0	+	+	+	+
Cyprinin (carp) .	—	8.7	0.0	30.3		—	—	—	—	—	—	—
Cyclopterin (*Cyclopterus lumpus*) . .	—	67.7	0.0	—		2.2	+	—	—	—	—	—
Crenilabrin (cunner)	0	42.3	0.0	11.9	25.1	+	0	—	—	—	—	

PER CENT OF GLUTAMIC ACID YIELDED BY PROTEINS

Proteins Soluble in Alcohol	
Gliadin (wheat)	42.98
Gliadin (rye)	37.80
Hordein (barley)	43.19
Zein (maize)	26.17
Albumins	
Leucosin (wheat)	5.72
Glutelins	
Glutenine (wheat)	23.40
Animal Proteins	
Casein (cow)	10.77
Ovalbumen (egg)	9.01
Conalbumin (egg)	7.00
Vitellin (egg yolk)	12.95
Serum albumen (horse)	7.70
Serum globulin (horse)	8.50
Halibut muscle	10.13
Chicken muscle	16.48
Scallop muscle	14.88
Dog tissues, entire body	14.00
Rabbit tissues, entire body	14.14
Hen tissues, entire body	12.02
Globulins	
Amandin (almond)	23.14
Edestin (hemp seed)	14.00
Corylin (hazel nut)	17.94
Phaseolin (bean)	12.33
Vignin (pea, bean)	16.39
Legumin (vetch)	16.48
Glycinine (soy bean)	19.46
Conglutin (yellow lupine)	30.05

260. The Fischer Ester Method for the Analysis of Proteins. — This method represents the most complex manipulation of the cleavage products of protein hydrolysis with a view to their separation in a pure form. After hydrolysis with strong acid, the amino acids are converted into their ethyl esters and the mixture of these is distilled under very diminished pressure. In this manner the amino acids are separated into several fractions each of which is much less complex than the original mixture. The esters are then saponified and subjected to an elaborate system of fractional crystallization either of the free amino acids or of certain of their salts.

The results obtained by the Fischer ester method are not quantitative for several reasons. The amino acids are partly lost in the elaborate treatment to which they are subjected. The esters of some of them are not volatile without decomposition, and the final separation of the components of the several fractions obtained on distillation of the esters is only partial.

The method is of the greatest value for the preparation of pure samples of certain of the amino acids, and led to the discovery of proline and oxyproline. It is rarely possible to account in the form of pure amino acids for more than half of the total nitrogen of the protein which is analyzed. The results obtained are not significant enough to make it possible to deduce from them any conclusions as to the biological value of the proteins as food.

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